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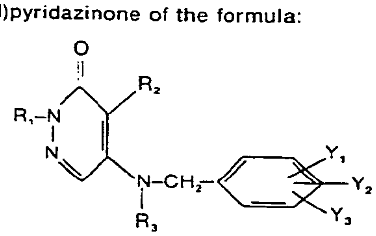
(54) **3(2H)pyridazinone, process for its preparation and anti-allergic agent containing it.**

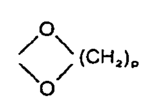
(57) A 3(2H)pyridazinone of the formula:



wherein R_1 is C_2–C_5 alkyl; R_2 is hydrogen, C_1–C_3 alkyl, chlorine or bromine; R_3 is hydrogen or C_1–C_4 alkyl; and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1–C_8 alkyl, C_2–C_8 alkenyl, halogen, $-(CH_2)_lA$ [wherein A is substituted amino of the formula $-N(R_4)(R_5)$ (wherein each of R_4 and R_5 which may be the same or different, is C_1–C_4 alkyl, or R_4 and R_5 together form C_4–C_6 alkylene), morpholino, 4-R_6-piperazin-1-yl (wherein R_6 is C_1–C_3 alkyl) or $-OR_7$ (wherein R_7 is hydrogen or C_1–C_3 alkyl), and l is an integer of 0 to 3], $-OR_8$ [wherein R_8 is hydrogen, C_1–C_8 alkyl, C_3–C_5 alkenyl, benzyl or $-(CH_2)_q$-R_9 [wherein R_9 is CO_2R_3 (wherein R_3 is as defined above), $-CONHR_3$ (wherein R_3 is as defined above) or $-CH_2OR_7$ (wherein R_7 is as defined above), and q is an integer of 1 to 5]], $-CO_2R_3$ (wherein R_3 is as defined above), $-CON(R_{10})(R_{11})$ [wherein each of R_{10} and R_{11} which may be the same or different, is hydrogen, C_1–C_4 alkyl or C_3–C_5 alkenyl, or R_{10} and R_{11} together form C_4–C_6 alkylene, $-(CH_2)_2O(CH_2)_2-$ or $-(CH_2)_2N(R_6)(CH_2)_2-$ (wherein R_6 is as defined above)], $-CONH(CH_2)_mA$ (wherein A is as defined above, and m is an integer of 2 to 4), $-CH=CHCOR_{12}$ (wherein R_{12} is hydroxy, C_1–C_4 alkoxy or $-N(R_{13})(CH_2)_nCO_2R_3$ (wherein R_{13} is hydrogen, C_1–C_6 alkyl or cycloalkyl, R_3 is as defined above, and n is an integer of 1 to 4)), $-SR_{14}$ (wherein R_{14} is C_1–C_4 alkyl),

$$-CN \text{ or } \underset{\underset{O}{\|}}{-C}R_3$$

(wherein R_3 is as defined above), or two of Y_1, Y_2 and Y_3 together form



(wherein p is an integer of 1 or 2), and a pharmaceutically acceptable salt thereof.

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3(2H)PYRIDAZINONE, PROCESS FOR ITS PREPARATION AND ANTI-ALLERGIC AGENT CONTAINING IT

The present invention relates to a 3(2H)pyridazinone which exhibits antagonism against slow reacting substance of anaphylaxis (SRS-A) which induces a contraction of bronchial smooth muscle, and thus is useful as an anti-allergic agent, a process for its preparation and a pharmaceutical composition containing it.

SRS-A is believed to be a principal etiologic substance which induces immediate allergy such as bronchial asthma or allergic rhinitis. Therefore, a medicine which controls the pharmacological effect of SRS-A, i.e. a SRS-A antagonist, is expected to be a useful anti-allergic agent.

However, a very few medicinal substances show antagonism against SRS-A, and no instance of their practical application has been reported.

As an example of a compound which is somewhat similar to the compound of the present invention, Chemical

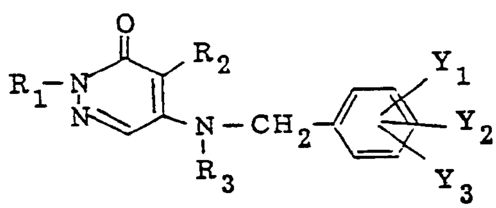
Abstract, 78. 4639 dg (U.S. Patent 374816) (hereinafter referred to as reference (a)) discloses 2-C_1-C_8-alkyl-4-chloro or bromo-5-benzylamino-3(2H)pyridazinone derivatives. However, the usefulness of the compounds disclosed in this reference (a) is restricted to a herbicide, and no mention is made as to its medical use or pharmacological activities.

As another example of a compound similar to the compound of the present invention, Chemical Abstract, 62, 2773b, (Bull. Soc. Chim, France, 1964 (9) p 2124-32) (reference (b)) discloses 2-methyl-4-chloro or bromo-5-benzylamino-3(2H)pyridazinones. This reference (b) is silent about medical use or pharmacological activities.

Likewise, as still another example of a compound similar to the compound of the present invention, published German Patent Application No. 1670169 (published on November 5, 1970) (reference (c)) discloses 2-alkyl-4-chloro-5-arylalkylamino-3(2H)pyridazinones. This reference (c) discloses a process for the synthesis of pyridazinones including such compounds, their application for agricultural chemicals, their application as intermediates for medicines or dyestuffs, or their application as intermediates for various compounds. However, no mention is made to their pharmacological activities, and no specific examples are given for such compounds. Further, such compounds are not specifically described.

The present inventors have synthesized and studied various compounds for antagonistic activities against SRS-A, and it has been surprisingly found that 3(2H)pyridazinones of the formula I and their pharmaceutically acceptable salts exhibit antagonistic activities against SRS-A and thus are useful as an active ingredient for an anti-allergic agent.

Namely, the present invention provides a 3(2H)pyridazinone of the formula:



(I)

wherein R_1 is C_2-C_5 alkyl; R_2 is hydrogen, C_1-C_3 alkyl, chlorine or bromine; R_3 is hydrogen or C_1-C_4 alkyl; and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, halogen, $-(CH_2)_{\ell}A$ [wherein A is substituted amino of the formula $-N(R_4)(R_5)$ (wherein each of R_4 and R_5 which may be the same or different, is C_1-C_4 alkyl, or R_4 and R_5 together form C_4-C_6 alkylene), morpholino, 4-R_6-piperazin-1-yl (wherein R_6 is C_1-C_3 alkyl) or $-OR_7$ (wherein R_7 is hydrogen or C_1-C_3 alkyl), and ℓ is an integer of 0 to 3], $-OR_8$ [wherein R_8 is hydrogen, C_1-C_8 alkyl, C_3-C_5 alkenyl, benzyl or $-(CH_2)_q-R_9$ [wherein R_9 is CO_2R_3 (wherein R_3 is

as defined above), $-CONHR_3$ (wherein R_3 is as defined above) or $-CH_2OR_7$ (wherein R_7 is as defined above), and q is an integer of 1 to 5]], $-CO_2R_3$ (wherein R_3 is as defined above), $-CON(R_{10})(R_{11})$ [wherein each of R_{10} and R_{11} which may be the same or different, is hydrogen, C_1-C_4 alkyl or C_3-C_5 alkenyl, or R_{10} and R_{11} together form C_4-C_6 alkylene, $-(CH_2)_2O(CH_2)_2-$ or $-(CH_2)_2N(R_6)(CH_2)_2-$ (wherein R_6 is as defined above)], $-CONH(CH_2)_mA$ (wherein A is as defined above, and m is an integer of 2 to 4), $-CH{=}CHCOR_{12}$ (wherein R_{12} is hydroxy, C_1-C_4 alkoxy or $-N(R_{13})(CH_2)_nCO_2R_3$ (wherein R_{13} is hydrogen, C_1-C_6 alkyl or cycloalkyl, R_3 is as defined above, and n is an integer of 1 to 4)), $-SR_{14}$ (wherein R_{14} is C_1-C_4 alkyl), -CN or $-\underset{\underset{O}{\|}}{C}R_3$ (wherein R_3 is as defined above), or two of Y_1, Y_2 and Y_3 together form $\genfrac{}{}{0pt}{}{-O\diagdown}{-O\diagup}(CH_2)_p$ (wherein p is an interger of 1 or 2), and a pharmaceutically acceptable salt thereof.

Now, the present invention will be described with reference to the preferred embodiments.

Specific examples of substituents R_1, R_2, R_3, Y_1, Y_2 and Y_3 will be described. However, it should be understood that the present invention is by no means restricted to such specific examples.

R_1 is ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl or i-pentyl;

R_2 is hydrogen, methyl, ethyl, n-propyl, i-propyl, chlorine or bromine;

R_3 is hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or sec-butyl; and

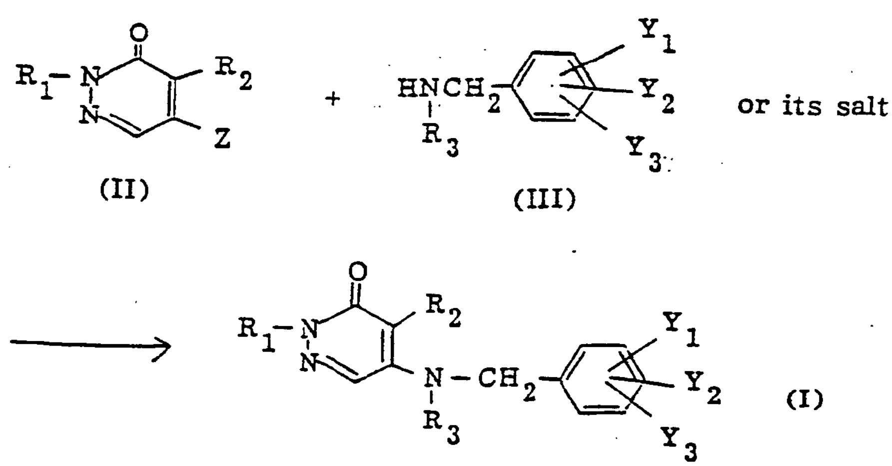
Each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, vinyl, 1-propenyl, 1-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl, fluorine, chlorine, bromine, iodine, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, dimethylaminomethyl, diethylaminomethyl, di-n-propyl-aminomethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl, 2-di-n-propylaminoethyl, dimethylaminopropyl, diethylaminopropyl, di-n-propylaminopropyl, morpholino, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 1-pyrrolidinyl, piperidino, hydroxy, methoxy, ethoxy, n-propoxy, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, methoxymethyl, 2-methoxyethyl, ethoxymethyl, 2-ethoxyethyl, n-buthoxy, i-butoxy, sec-butoxy, n-pentyloxy, i-pentyloxy, n-hexyloxy, allyloxy, 3-butenyloxy, 2-butenyloxy, 4-pentenyloxy, 2-pentenyloxy, n-heptyloxy, n-octyloxy, benzyloxy, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, sec-butylthio, carboxymethyloxy, methoxycarbonylmethyloxy, ethoxycarbonylmethyloxy, n-propoxycarbonylmethyloxy, 2-carboxyethyloxy, 2-methoxycarbonylethyloxy, 2-ethoxycarbonylethyloxy, 3-carboxypropyloxy,

3-methoxycarbonylpropyloxy, 3-ethoxycarbonylpropyloxy, 4-carboxybutyloxy, 4-methoxycarbonylbutyloxy, 4-ethoxycarbonylbutyloxy, 5-carboxypentyloxy, 5-methoxycarbonylpentyloxy, 5-ethoxycarbonylpentyloxy, carbamoylmethyloxy, methylaminocarbonylmethyloxy, ethylaminocarbonylmethyloxy, n-propylaminocarbonylmethyloxy, 2-(carbamoyl)ethyloxy, 2-(methylaminocarbonyl)ethyloxy, 2-(ethylaminocarbonyl)ethyloxy, 2-(n-propylaminocarbonyl)ethyloxy, 3-(carbamoyl)propyloxy, 3-(methylaminocarbonyl)propyloxy, 4-(carbamoyl)butyloxy, 4-(methylaminocarbonyl)butyloxy, 5-(carbamoyl)pentyloxy, 2-hydroxyethyloxy, 2-methoxyethyloxy, 2-ethoxyethyloxy, 2-propoxyethyloxy, 3-hydroxypropyloxy, 3-methoxypropyloxy, 3-ethoxypropyloxy, 4-hydroxybutyloxy, 4-methoxybutyloxy, 4-ethoxybutyloxy, 5-hydroxypentyloxy, 5-methoxypentyloxy, 5-ethoxypentyloxy, 6-hydroxyhexyloxy, 6-methoxyhexyloxy, 6-ethoxyhexyloxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, carbamoyl, methylaminocarbonyl, ethylaminocarbonyl, allylaminocarbonyl, n-propylaminocarbonyl, n-butylaminocarbonyl, morpoholinocarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-ethylpiperazin-1-ylcarbonyl, piperidinocarbonyl, 2-dimethylaminoethylaminocarbonyl, 2-diethylaminoethylaminocarbonyl, 2-(di-n-propylamino)-ethylaminocarbonyl, 2-piperidinoaminoethylcarbonyl, 3-dimethylaminopropylaminocarbonyl, 3-diethylaminopropylaminocarbonyl, 2-hydroxyethylaminocarbonyl,

2-methoxyethylaminocarbonyl, 2-ethoxyethylaminocarbonyl, 3-hydroxypropylaminocarbonyl, 3-methoxypropylaminocarbonyl, 3-ethoxypropylaminocarbonyl, 2-carboxyethenyl, 2-methoxycarbonylethenyl, 2-ethoxycarbonylethenyl, 2-(carboxymethylaminocarbonyl)ethenyl, 2-(methoxycarbonylmethylaminocarbonyl)ethenyl, 2-(ethoxycarbonylmethylaminocarbonyl)ethenyl, 2-(2-carboxyethylaminocarbonyl)ethenyl, 2-(2-methoxycarbonylethylaminocarbonyl)ethenyl, 2-(2-ethoxycarbonylethylaminocarbonyl)ethenyl, 2-(3-carboxypropylaminocarbonyl)ethenyl, 2-(3-methoxycarbonylpropylaminocarbonyl)ethenyl, cyano, formyl, acetyl or propionyl, or two of Y_1, Y_2 and Y_3 may together form $-OCH_2O-$ or $-OCH_2CH_2O-$.

Now, a process for the production of the compound of the formula I of the present invention will be described. The compound of the formula I may be prepared by the following reaction scheme 1:

Reaction scheme 1

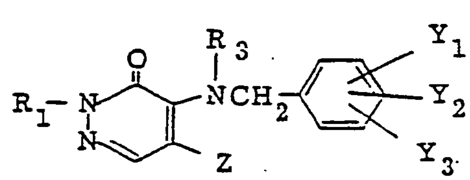


wherein R_1, R_2, R_3, Y_1, Y_2 and Y_3 are the same as defined above with respect to the formula I, and Z is chlorine or bromine.

Namely, the compound of the formula I can be prepared by reacting a 3(2H)pyridazinone compound of the formula II, i.e. one of starting materials, with a benzylamine derivative of the formula III or its acid salt in an inert solvent in the presence of a dehydrohalogenating agent.

As the solvent, there may be employed an ether solvent such as diethyl ether, isopropyl ether, tetrahydrofuran or 1,4-dioxane, an amide solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone, dimethyl sulfoxide, an alcohol solvent such as methanol, ethanol or 1-propanol, a hydrocarbon solvent such as toluene or benzene, a ketone solvent such as acetone or methyl ethyl ketone, an organic amine solvent such as pyridine or a trialkylamine, or water.

In the above reaction, if R_2 is chlorine or bromine, there will be formed, in addition to the compound of the formula I, a compound of the formula:



(IV)

wherein R_1, R_3, Z, Y_1, Y_2 and Y_3 are the same as defined above with respect to the formula I, which is an isomer of the compound of the formula I with the 5-position substituted by benzylamino, as a by-product. The production rates of the compounds of the formulas I and IV depend upon the polarity of a solvent used. Namely, if a solvent having high polarity, such as water, a lower alcohol, an ether, an amide or dimethyl sulfoxide is used, the production rate of the compound of the formula I tends to be high. On the other hand, if a hydrocarbon solvent such as toluene or benzene is used, the production rate of the compound of the formula IV tends to increase.

Accordingly, in order to efficiently obtain the compound of the formula I, it is preferred to use a solvent having high polarity as mentioned above or to use a solvent mixture of water and an organic solvent, as the case requires.

The compound of the formula I may readily be separated and purified by fractional crystallization or by means of silica gel column chromatography.

As the dehydrohalogenating agent to be used, there may be employed an inorganic base, for instance, potassium carbonate, sodium carbonate or sodium hydrogencarbonate, and an organic base, for instance, a tertiary amine such as N,N-dimethylaniline, N,N-diethylaniline, trimethylamine or triethylamine,

pyridine or methylethylpyridine. If necessary, a quarternary amine such as triethylbenzylammonium chloride may be added as an inter-phase transfer catalyst to the reaction system.

The reaction temperature may be within a range of from 10°C to the boiling point of the solvent used for the reaction.

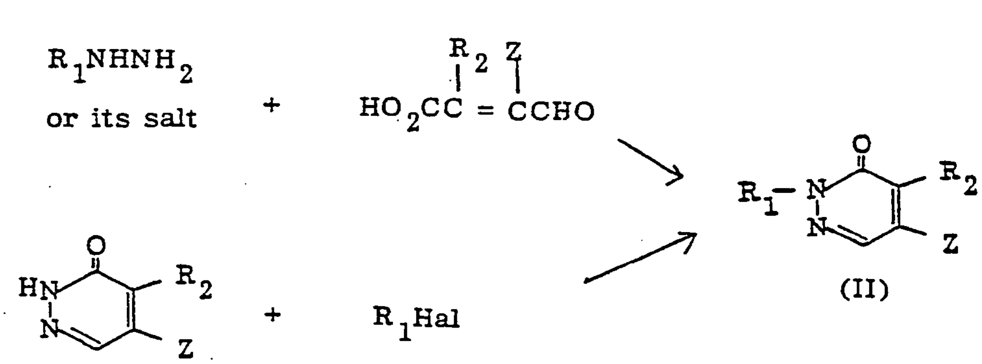
The molar ratios of the starting materials may optionally be set. However, it is common to use from 1 to 5 mols, preferably from 1 to 3 mols, of the benzylamine derivative of the formula III relative to 1 mol of the pyridazinone derivative of the formula II.

The 3(2H)pyridazinone compound of the formula II having a substituent at the 2-position, i.e. one of starting materials, wherein both R_2 and Z are the same and are chlorine or bromine, may be prepared by known processes as shown in reaction scheme 2 (for instance, Process 2-1 disclosed in Advances in Heterocyclic Chemistry, Vol. 9, p. 257(1968) or Process 2-2 disclosed in Chemical Abstract, 62, 2772g).

Reaction scheme 2

2-1

2-2

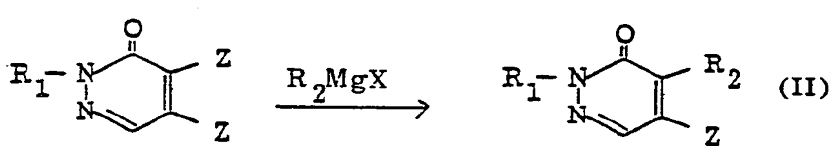


wherein R_1 is the same as defined above with respect to the formula I, and both R_2 and Z are chlorine or bromine.

Process 2-1 is a reaction for the production of the compound of the formula II by the ring closure reaction of a hydrazine or its acid salt with a mucochloric acid or mucobromic acid. Process 2-2 is a reaction for the production of the compound of the formula II by reacting 4,5-(dichloro or bromo)-3(2H)pyridazinone with a compound of the formula R_1-Hal (wherein R_1 is alkyl, and Hal is chlorine, bromine or iodine). For the production of the compound of the formula II, Process 2-1 or Process 2-2 may optionally be selected. While it is advantageous to employ Process 2-1 from the viewpoint of the yield and operation efficiency, it is usually advantageous to employ Process 2-2 when a hydrazine is commercially hardly available or difficult to produce economically.

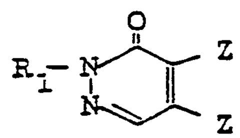
The compound of the formula II wherein R_2 is C_1-C_3 alkyl, may be prepared by a process as shown in reaction scheme 3 or 4.

Reaction scheme 3



wherein R_1 and Z are the same as defined above with respect to the formula II, X is bromine or iodine, and R_2 is C_1-C_3 alkyl.

Namely, such a compound may readily be prepared by reacting a 2-alkyl-4,5-di-(chloro or bromo)-3(2H)-pyridazinone of the formula:

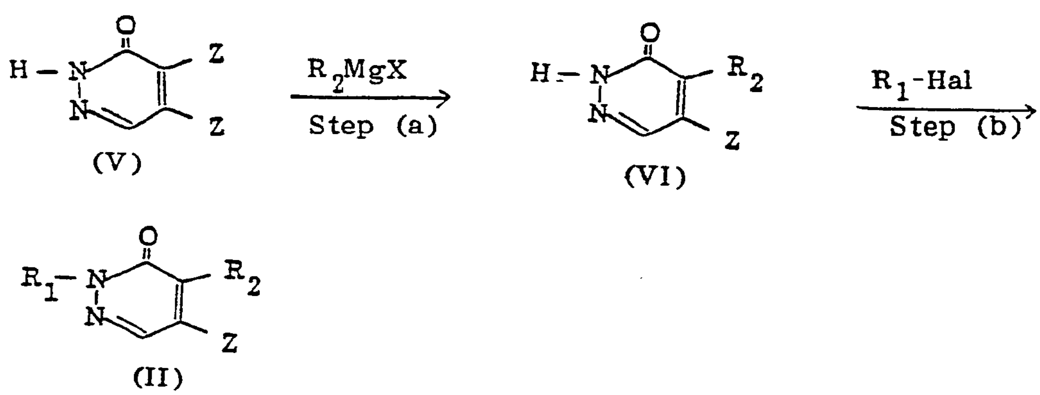


with a Grignard reagent of the formula R_2MgX in the presence of an inert gas. As the solvent, there may be employed a hydrocarbon solvent such as toluene or benzene, and an ether solvent such as tetrahydrofuran or ethyl ether.

The reaction temperature may be within a range of from 0^oC to the boiling point of the solvent used for the reaction.

The molar ratios of the starting materials may optionally be set. However, it is common to use from 1 to 5 mols, preferably from 1 to 3 mols, of the Grignard reagent relative to 1 mol of the 4,5-di-(chloro or bromo)-3(2H)pyridazinone.

Reaction scheme 4

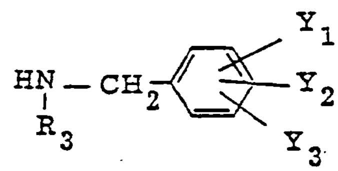


wherein R_1 and R_2 are the same as defined above with respect to reaction scheme 3, and Hal is the same as defined above with respect to Process 2-2.

Namely, the compound of the formula II may also be obtained by reacting 4,5-di-(chloro or bromo)-3(2H)-pyridazinone of the formula V having no substituent at the 2-position with a Grignard reagent of the formula R_2MgX to obtain a compound of the formula VI, and reacting the compound of the formula VI with an alkyl halide of the formula R_1Hal.

Step (a) may be conducted under the conditions similar to those of the reaction scheme 3. Likewise, Step (b) may be conducted in the same manner as in reaction scheme 2-2.

With respect to the other starting material, i.e. a benzylamine of the formula:

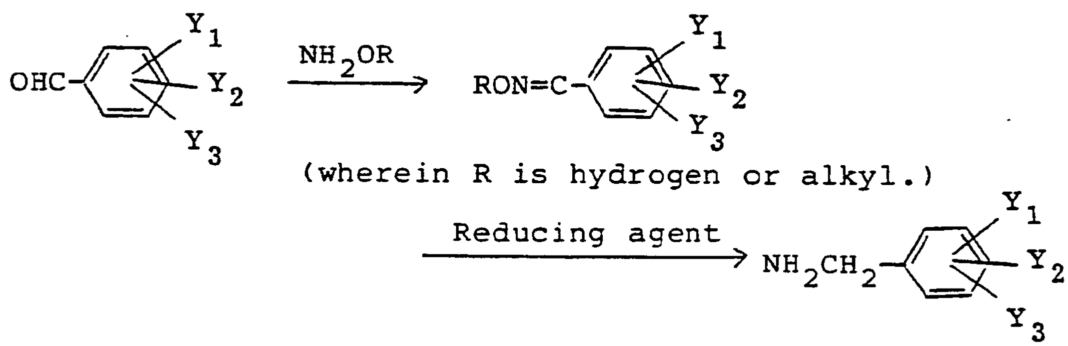


wherein R_3, Y_1, Y_2 and Y_3 are as defined above, the one which is hardly available as a commercial product, may be prepared by a known process for the preparation of a benzylamine as shown by reaction scheme 5.

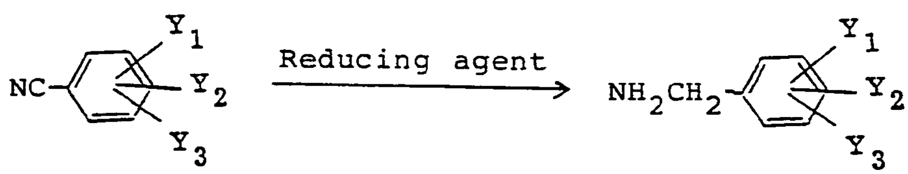
Reaction scheme 5

Processes for the preparation of various benzylamines

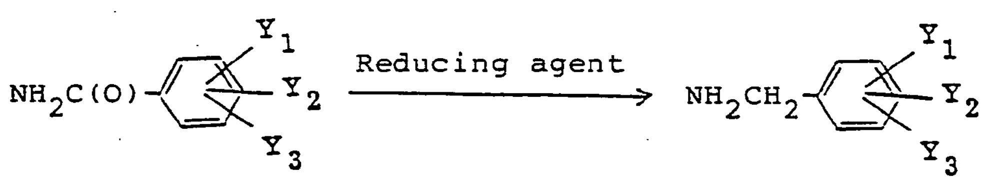
(A)



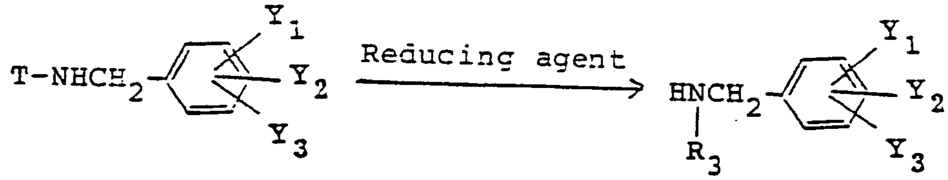
(B)



(C)

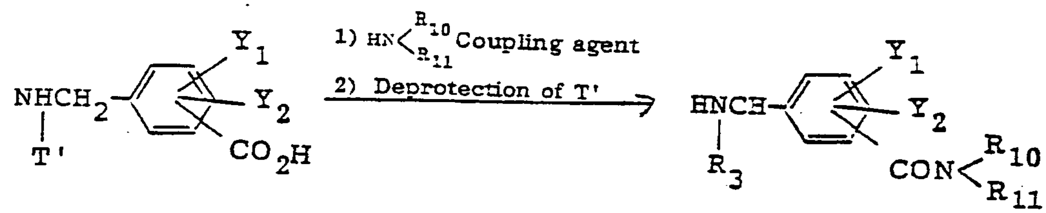


(D)



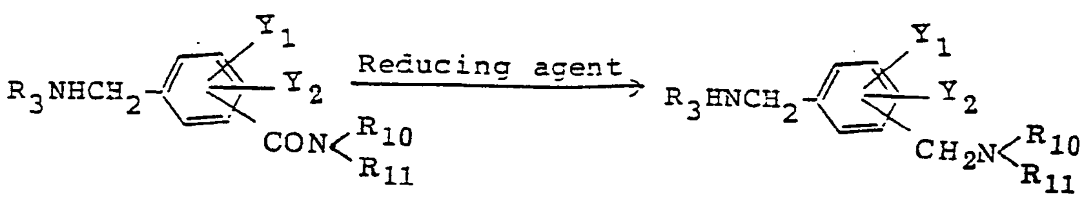
(wherein T is C_2-C_4 acyl or alkoxycarbonyl such as ethoxycarbonyl or t-butoxycarbonyl.)

(E)



(wherein R_{10} and R_{11} are as defined above, and T' is alkoxycarbonyl such as ethoxycarbonyl or t-butoxy-carbonyl.)

(F)



(wherein R_{10} and R_{11} are as defined above.)

In each of processes A, B and C, the desired benzylamine is prepared by the treatment of the starting material with a reducing agent. The starting material is an intermediate aldoxime prepared by reacting the corresponding aldehyde with hydroxyamine or alkoxyamine in the case of Process A, the corresponding nitrile in the case of Process B, or the corresponding amide in the case of Process C. In Process D, the desired N-alkyl substituted benzylamine is prepared by the treatment of

the corresponding N-acyl substituted or N-alkoxycarbonyl substituted benzylamine with a reducing agent.

Any one of Processes A to D may optionally be employed by using a commercially available product or a starting material derived from such a commercial product. As a method for reduction, there is known (1) a method wherein Raney nickel (nickel-aluminum alloy) is used in the presence of an alkali metal hydroxide such as sodium hydroxide, or (2) a method wherein sodium borohydride is used in the presence of an acid such as acetic acid, trifluoroacetic acid or Lewis acid. A proper method for reduction is selected taking into account the substituents Y_1, Y_2 and Y_3 on the phenyl ring, the economy and the chemical stability. For instance, the reduction method (1) is suitable when the substituents Y_1, Y_2 and Y_3 have a substituent such as alkyl or alkoxy which is durable against a relatively strong reducing agent. Whereas, the reduction method (2) which is a relatively mild reduction method, is suitable when the substituents have a relatively unstable substituent such as a halogen, an olefin, an ester, an amine or an amide.

Process E is directed to the preparation of a benzylamine derivative having an amide bond by reacting a benzylamine having CO_2H as a substituent with a dehydrating condensation agent such as N,N'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide or ethyl chlorocarbonate.

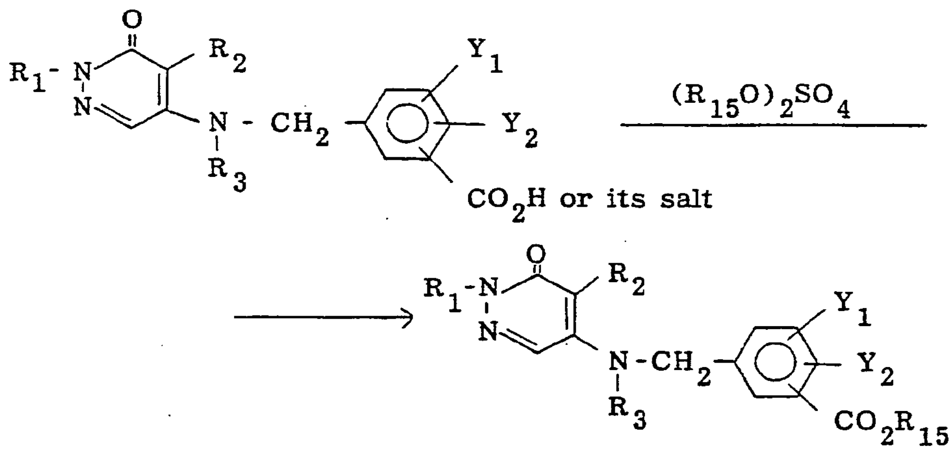
Process F is directed to the preparation of a benzylamine having a substituted aminoalkyl group on the

phenyl ring by treating a benzylamine derivative obtained by e.g. Process E with a reducing agent such as lithium aluminum hydride.

In general, a benzylamine reacts with carbon dioxide in air to form a carbonate. Therefore, for its isolation, it is advantageous, in most cases, to obtain it in the form of an acid salt such as a hydrochlorate or a sulfate. A hydrochlorate of benzylamine may be subjected by itself to the reaction with 4,5-di-(chloro or bromo-)-3(2H)pyridazinone.

The compound of the formula I wherein one, two or three of the substituents Y_1, Y_2 and Y_3 are $-CO_2R_{15}$ (wherein R_{15} is C_1-C_4 alkyl), may readily be prepared by esterifying a compound having the corresponding carboxyl group or its salt with a dialkyl sulfuric acid ester of the formula $(R_{15}O)_2SO_4$ (wherein R_{15} is C_1-C_4 alkyl) in the presence of an acid-binding agent such as sodium hydroxide, potassium hydroxide, potassium or sodium carbonate or bicarbonate, or an organic amine, as shown in reaction scheme 6.

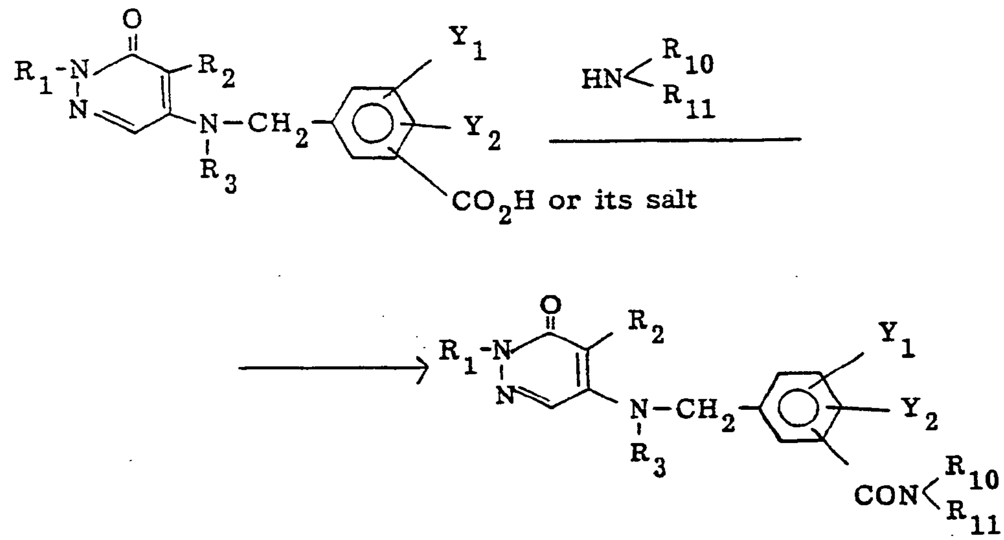
Reaction scheme 6



(wherein R_1, R_2, R_3, Y_1, Y_2 and R_{15} are the same as defined above with respect to the formula I.)

The compound of the formula I wherein one, two or three of the substituents Y_1, Y_2 and Y_3 are $-CON(R_{10})(R_{11})$, may readily be prepared by dehydrating and condensing a compound having the corresponding carboxyl group or its salt with $HN(R_{10})(R_{11})$ in the presence of a dehydrating condensation agent such as N,N'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide or ethyl chlorocarbonate, as shown in reaction scheme 7.

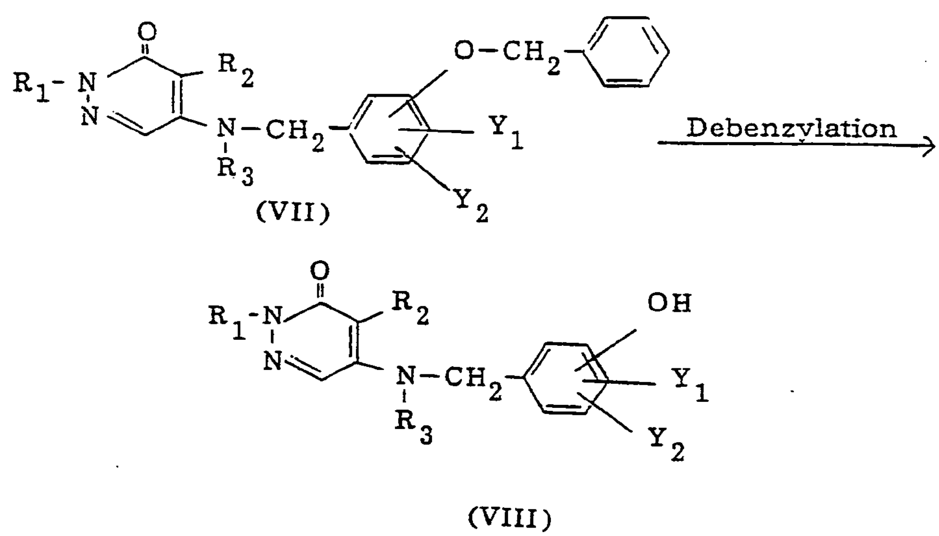
Reaction scheme 7



(wherein R_1, R_2, R_3, R_{10}, R_{11}, Y_1 and Y_2 are the same as defined above with respect to the formula I.)

The compound of the formula I wherein one, two or three of the substituents Y_1, Y_2 and Y_3 are hydroxyl groups, may be prepared by directly reacting the corresponding benzylamine with the 3(2H)pyridazinone of the formula II. However, it may also readily be prepared by debenzylating a compound of the formula VII having the corresponding benzyloxy group by means of catalytic hydrogenation procedure generally used, hard acid (e.g. hydrogen chloride, trifluoroacetic acid) treatment, or a combination of a soft base with a hard acid (e.g. a combination of dimethyl sulfide with boron trifluoride), as shown in reaction scheme 8.

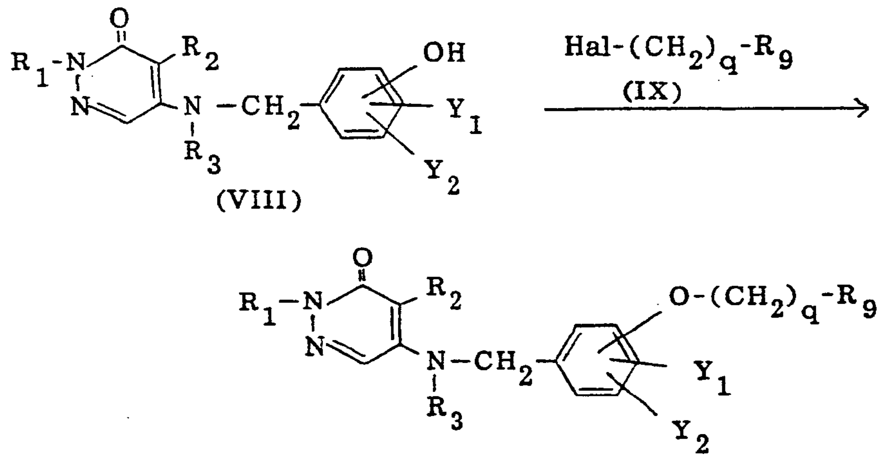
Reaction scheme 8



(wherein R_1, R_2, R_3, Y_1 and Y_2 are the same as defined above with respect to the formula I.)

Likewise, a compound of the formula X having $-O-(CH_2)_q-R_9$ (wherein R_9 and q are the same as defined above with respect to the formula I) may be prepared by reacting a compound of the formula VIII obtained by reaction scheme 8 with $Hal-(CH_2)_q-R_9$ of the formula IX (wherein Hal is the same as difined above with respect to reaction scheme 2-2 and R_9 is as defined above), as shown in reaction scheme 9.

Reaction scheme 9



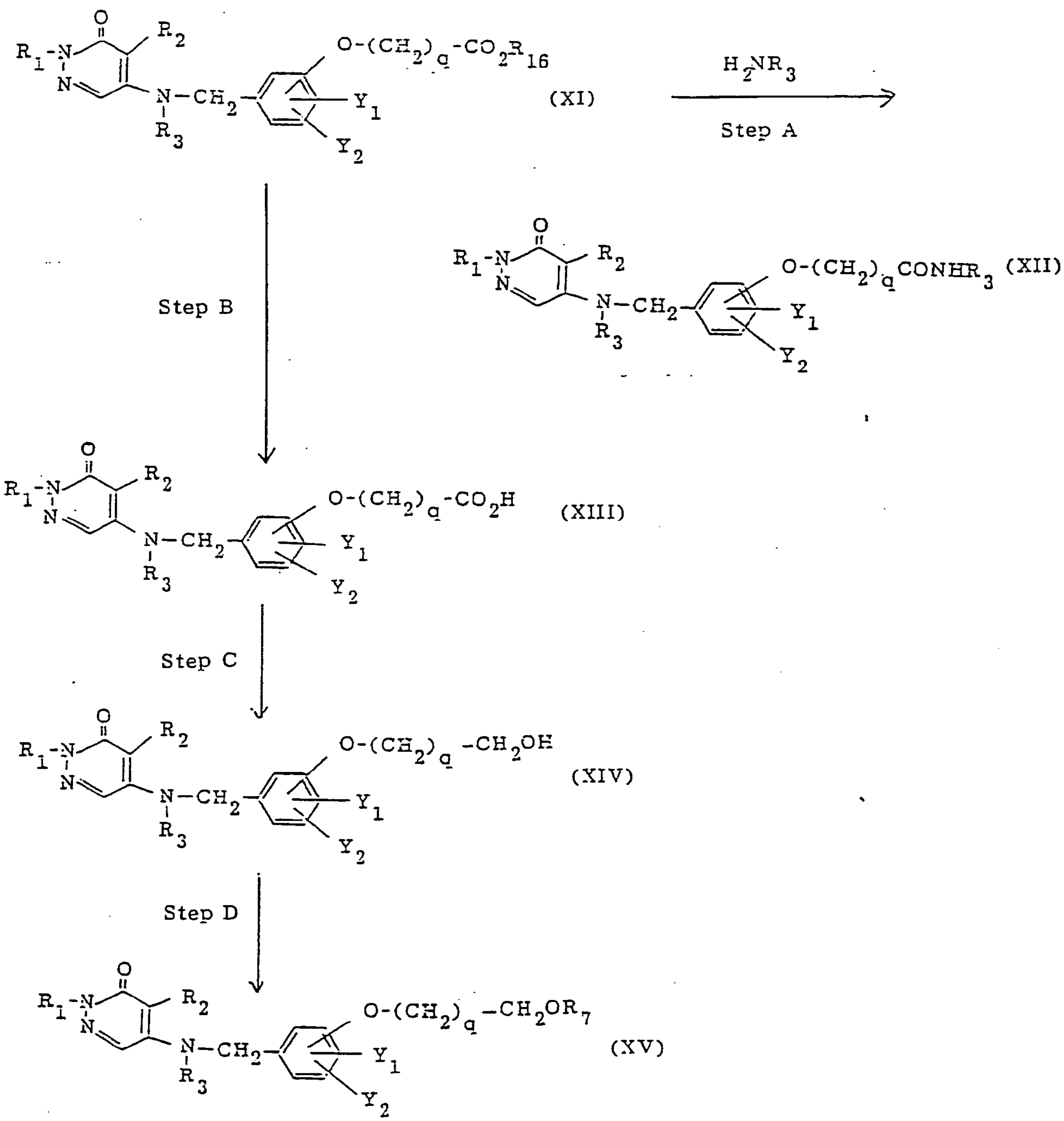
(VIII)

(X)

(wherein Hal is as defined above, and R_1, R_2, R_3, R_9, Y_1, Y_2 and q are the same as defined above with respect to the formula I.)

Alternatively, the object may also be attained by subjecting a compound of the formula XI, i.e. one of compounds obtained by the method of reaction scheme 9, to a usual organic reaction whereby the functional group R_9 is converted. One of specific examples will be shown in reaction scheme 10.

Reaction scheme 10

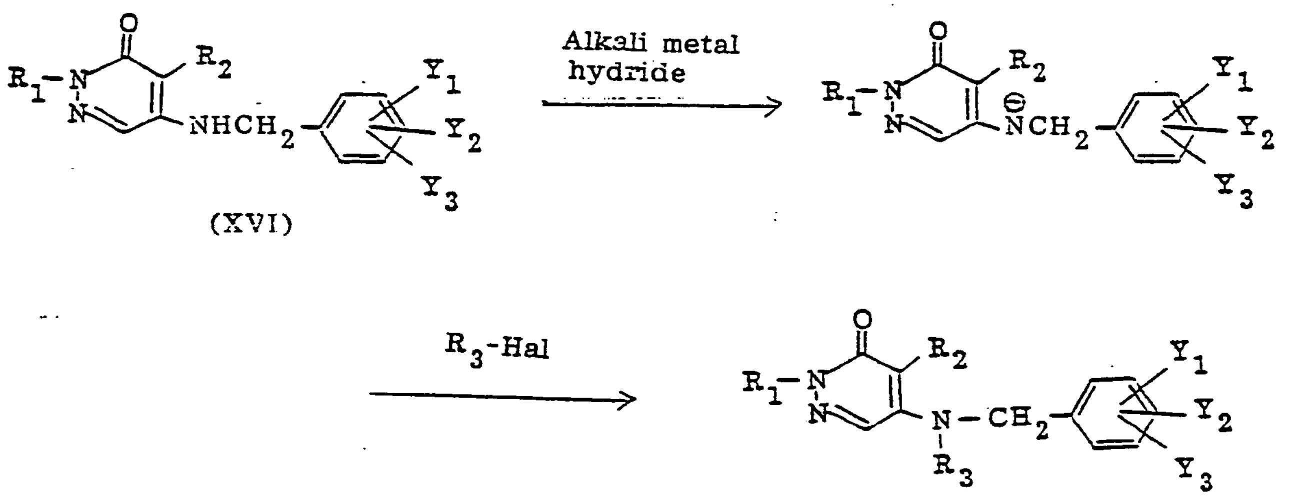


(wherein R_1, R_2, R_3, R_7, Y_1, Y_2, Y_3 and q are the same as defined above with respect to the formula I, and R_{16} is C_1-C_4 alkyl.)

Step A is a process for preparing an amide of the formula XII by reacting $-CO_2R_{16}$ of the compound of the formula XI with H_2NR_3. Step B is a process for converting a compound of the formula XI to a carboxylic acid of the formula XIII by hydrolyzing it with a usual acid or alkali. Step C is a process for converting the carboxyl group of the compound of the formula XIII obtained in Step B to the alcohol of a compound of the formula XIV with a reducing agent such as sodium-bis-methoxyethoxyaluminum halide. Step D is a process for preparing a compound of the formula XV by alkylating the compound of the formula XIV obtained in Step C with e.g. an alkyl halide. (Specific manners for the respective steps will be given in Examples 5A-11A.)

The compound of the formula I wherein R_3 is C_1-C_3 alkyl, may readily be prepared by reacting a compound of the formula XVI with a metal hydride and then reacting the product with an alkyl halide of the formula: R_3-Hal (wherein R_3 and Hal are as defined above), as shown in reaction scheme 11.

Reaction scheme 11

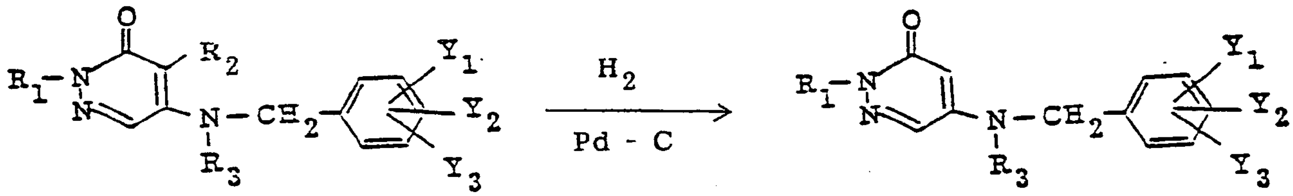


(wherein R_1, R_2, R_3, Y_1, Y_2 and Y_3 are the same as defined above with respect to the formula I, and Hal is as defined above.)

As the organic solvent to be used, it is preferred to use an inert organic solvent such as dimethylformamide or tetrahydrofuran. As the alkali metal hydride, sodium hydride is preferred. The reaction temperature is preferably within a range of from -40 to 10°C in the case of the reaction with an alkali metal hydride, and within a range of from -15 to 70°C in the case of the reaction with an alkyl halide.

The compound of the formula I wherein R_2 is hydrogen, may readily be prepared by dehalogenating the corresponding compound of the formula XVII wherein R_2 is chlorine by a hydrogen addition method (a common hydrogen addition method wherein palladium-carbon is used as a catalyst), as shown in reaction scheme 12.

Reaction scheme 12



(XVII)

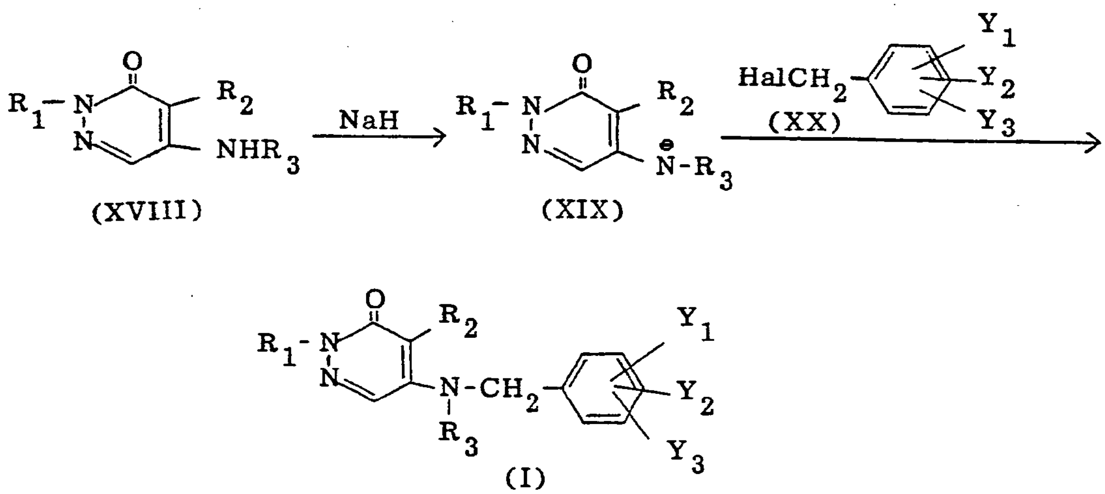
(wherein R_1, R_2, R_3, Y_1, Y_2 and Y_3 are the same as defined with respect to the formula I.)

As the organic solvent to be used, a usual inert solvent may be employed. However, it is particularly preferred to employ an alcohol solvent such as ethanol or methanol. An organic amine such as triethylamine or pyridine may be added whereby the reaction proceeds smoothly. The reaction temperature may be within a range of from 10°C to the boiling point of the organic solvent used, but it is preferably within a range of from 20 to 60°C.

The compound of the formula I may readily be prepared by reacting 3(2H)pyridazinone of the formula XVIII having $-NHR_3$ (wherein R_3 is as defined above) at the 5-position with a benzyl halide of the formula XX or its derivative, as shown in reaction scheme 13. Namely, the compound of the formula I may also be prepared by reacting the 3(2H)pyridazinone of the formula XVIII with an alkali metal hydride such as sodium hydride in a solvent such as DMF or an ether solvent at a temperature of from 0 to

10°C to form the corresponding anion compound of the formula XIX, and then reacting it with a benzyl halide of the formula XX.

Reaction scheme 13



(wherein R_1, R_2, R_3, Y_1, Y_2, Y_3 and Hal are as defined above.)

The reaction may be conducted in the same conditions as those in reaction scheme 11.

Specific examples of the compounds covered by the present invention are, in addition to compounds described in Examples later in this specification, as follows:

4-chloro-5-(3-methoxycarbonyl-4-methoxybenzylamino)-2-t-butyl-3(2H)pyridazinone;

2,4-diethyl-5-(3,4-dimethoxybenzylamino)-3(2H)-pyridazinone;

4-chloro-5-(2-bromobenzylamino)-2-n-propyl-3(2H)-pyridazinone;

4-chloro-5-(3-n-pentyloxy-4-hydroxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-chloro-5-(3-n-pentyloxy-4-hydroxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-chloro-5-(3-methoxy-4-hydroxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-chloro-5-(3-methoxy-4-hydroxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-chloro-5-(3-methoxy-4-hydroxybenzylamino)-2-n-propyl-3(2H)pyridazinone;

4-chloro-5-(4-cis-1-heptenylbenzylamino)-2-ethyl-3(2H)pyridazinone;

4-methyl-5-(2,4-dimethylbenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-methyl-5-(3-ethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-methyl-5-(3-ethoxy-4-methoxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-methyl-5-(3-n-propoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-methyl-5-(3-n-propoxy-4-methoxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-ethyl-5-(2,4-dimethylbenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-ethyl-5-(2,4-dimethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-ethyl-5-(3-ethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-ethyl-5-(3-ethoxy-4-methoxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-ethyl-5-(3-n-propoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-ethyl-5-(3-n-propoxy-4-methoxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-n-propyl-5-(2,4-dimethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-methyl-5-(2,4-dimethylbenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-methyl-5-(2,4-dimethoxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-methyl-5-(3-ethoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-methyl-5-(3-n-propoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-ethyl-5-(2,4-dimethoxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-ethyl-5-(4-methoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone;

4-ethyl-5-(3-ethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone;

4-ethyl-5-(3-ethoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone;

4-n-propyl-5-(2,4-dimethoxybenzylaminc)-2-i-propyl-3(2H)pyridazinone;

4-n-propyl-5-(3-methoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone;

4-n-propyl-5-(4-methoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone;

4-n-propyl-5-(3-ethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone;

4-chloro-5-(3,4-diethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone;

4-chloro-5-(3-n-propoxy-4-ethoxybenzylamino)-2-ethyl-3(2H)pyridazinone;

4-chloro-5-(3,4-diethoxybenzylamino)-2-i-propyl-3(2H)pyridazinone

TEST EXAMPLES

A. Anti-allergic activities

A major constituent of SRS-A which is an important mediator for immediate allergy such as bronchoconstiriction in bronchial asthma, has already been found to be leukotriene C_4 (hereinafter referred to as LTC_4), leukotriene D_4 (hereinafter referred to as LTD_4) or the like. Accordingly, antagonistic activities against SRS-A can be evaluated by any one of the following test methods:

(1) a method of examining the antagonistic activities against SRS-A obtained from a sensitized guinea-pig,

(2) a method of examining the antagonistic activities against LTC_4, and

(3) a method of examining the antagonistic activities against LTD_4.

The present inventors examined the antagonistic activities against SRS-A by using the test methods (1) to (3).

Now, the test methods and the results will be described.

Test methods of anti-allergic activities and the results

(i) SRS-A antagonism in guinea-pig ileum

SRS-A antagonism was determined against the contraction induced by SRS-A in isolated guinea-pig ileum. The SRS-A was prepared in accordance with the method of Brocklehurst (J. Physiol., 151, 416, 1960) and Kohno and Parker (J. Immunol., 125, 446, 1980). Adult male guinea-pigs (200-250 g) were sensitized with chick egg albumin (EA), 100 mg subcutaneously and 100 mg intraperitoneally. Three weeks later the animals were killed by a blow on the head and lungs were perfused free of blood with Tyrode solution passed through the right ventricle. Isolated lungs were chopped into pieces (1 mm^3) by a scissors in Tyrode solution and filtrated with gauze, and then 1.0-1.3 g of chopped lung fragments were distributed into individual tubes (9.7 ml of Tyrode solution/tube). EA solution (0.3 ml) at a 3×10^{-4} g/ml final concentration was added to the tubes and incubated for 20 min at 37°C, and then the supernatant was used for the SRS-A antagonism.

Assay for SRS-A antagonism was performed as follows: Ileum preparations isolated from male guinea-pig (300-400 g) were suspended under 0.5 g tension in organ baths (5 ml) containing Tyrode solution maintained at 30°C and gassed with 95% O_2 + 5% CO_2. After the repeated responses to histamine (10^{-7} g/ml) was established, the contractile response to SRS-A (0.5 ml) was carried out in the presence of 10^{-6} M atropine and 10^{-6} M pyrilamine. Test compounds dissolved in 100% dimethyl sulfoxide were added to the organ baths (final concentration of 5×10^{-7} g/ml) 1 min prior to the SRS-A addition, and SRS-A-induced contractions were compared with those of control (SRS-A-induced contraction before the treatment). The SRS-A antagonism (%) = [1.0 - (SRS-A-induced contraction in test compound)/control] x 100

SRS-A antagonism by test compounds (5×10^{-7} g/ml) are shown in Table 1.

Table 1

Test compound No.	Antagonism (%)	Test compound No.	Antagonism (%)
1	14	18	74
2	47	21	77
3	64	22	76
4	73	23	18
5	74	25	81
9	72	30	53
10	40	32	18
11	74	33	41
12	73	34	19
16	55	35	10
44	55	42	14
38	31	52	72
41	15	55	12
		FPL-55712 (Reference compound)	88

(ii) LTC$_4$ and LTD$_4$ antagonisms in guinea-pig trachea

Antagonism for LTC$_4$ and LTD$_4$ were determined in isolated guinea-pig trachea prepared as spiral strip. Tracheal preparations were suspended under 1 g tension in 10 ml organ baths and they were incubated for 1 hr prior to use. Contractile responses to LTC$_4$ (2 x 10^{-8} g/ml) and LTD$_4$ (2 x 10^{-8} g/ml) were obtained after the maximal response to histamine (10^{-4} M). Test compounds dissolved in 100% dimethyl sulfoxide were added to the organ baths (final concentration of 10^{-5} g/ml) 5 min prior to LTC$_4$ and LTD$_4$ addition, and then contractile responses to LTC$_4$ and LTD$_4$ were compared with those of control which was obtained from a paired trachea in the absence of test compounds. LTC$_4$- and LTD$_4$-induced contractions were expressed as a percentage of the maximal response to

histamine. The antagonism was determined as follows:
Antagonism (%) = (1.0 - % contraction in test/% contraction in control) x 100

LTC_4 antagonisms by test compounds (10^{-5} g/ml) are shown in Table 2.

Table 2

Test compound No.	Antagonism (%)	Test compound No.	Antagonism (%)
2	84	40	17
3	42	43	57
4	55	48	30
5	67	49	8
6	33	55	14
10	50	59	17
11	25	75	100
12	67	86	100
14	100	88	81
15	100	89	89
16	96	93	93
21	36	94	83
22	20	97	100
24	7	102	97
29	68	103	100
30	13	105	100
32	20	106	100
33	17	119	100
35	37	FPL-55712 (Reference compound)	100

LTD_4 antagonisms by test compounds (10^{-5} g/ml) are shown in Table 3.

Table 3

Test compound No.	Antagonism (%)	Test compound No.	Antagonism (%)
3	50	95	62
54	10	96	59
13	76	97	100
15	80	98	55
14	36	99	99
17	80	100	21
39	67	101	54
58	23	102	86
50	12	103	100
56	19	104	68
57	27	105	100
8	53	106	100
6	62	107	65
7	92	108	53
60	15	109	92
46	49	110	69
45	14	111	72
36	19	112	86
26	38	113	40
28	52	114	77
53	38	115	73
61	21	116	89
20	17	117	25
19	66	118	61
47	65	119	100
74	91	120	26
75	90	121	31
76	97	122	23
77	90	123	88
78	97	124	71
79	100	125	53
80	99	126	63
81	68	127	76
82	46	128	21
83	74	129	48
84	96	130	100
85	91	131	52
86	87	132	61
87	100	133	66
88	95	134	75
89	95	135	61
90	96	136	64
91	93	137	96
92	92	138	86
93	96	139	57
94	75	140	77

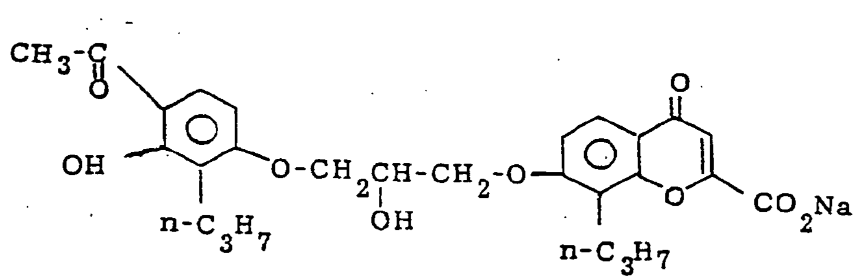
Table 3 (cont'd)

Test compound No.	Antagonism (%)	Test compound No.	Antagonism (%)
141	90	156	72
142	41	157	88
143	28	158	99
144	44	159	98
145	81	160	98
146	32	161	95
147	73	162	100
148	62	163	95
149	68	164	82
150	57	165	71
151	78	166	100
152	75	167	96
153	45	168	99
154	100	169	100
155	60		
		FPL-55712 (Reference compound)	88

(iii) <u>Effect on anaphylactic bronchoconstriction in passively sensitized guinea-pig</u>

Male guinea-pigs (350-450 g) were passively sensitized with intravenous (i.v.) injection of 0.125 ml rabbit anti-EA serum (Cappel Laboratories) 1 day preceding the experiment. Antigen-induced anaphylactic bronchoconstrictions were measured by modified method of Konzett and Rössler (Arch. Exp. Path. Pharmak., <u>195</u>, 71, 1940). Sensitized guinea-pigs were anaesthetized with intraperitoneal injection of urethane (1.5 g/kg). The right jugular vein was cannulated for the administration of the all agents and trachea was cannulated to record total pulmonary resistance. Guinea-pigs were artificially ventilated by a small animal respirator

(Shinano, Model SN-480-7) set at a stroke volume of 4-5 ml and a rate of 50 breaths per min. The change in pulmonary resistance was measured with a pressure transducer (Nihon Kohden, Model TP-602T) connected to a T-tube on the tracheal cannula. The increase in air overflow volume was expressed as a percentage of the maximum bronchoconstriction obtained by clamping off the trachea. Following surgical preparation, the animals were pretreated with indomethacin (1.0 mg/kg, 10 min), pyrilamine (2 mg/kg, 6 min) and propranolol (0.1 mg/kg, 5 min) prior to the EA challenge (0.1 or 10 mg/kg). All test compounds, 2 mg/kg in 3% Tween 80 or 3% PEG-400, were administered 1 min before the EA challenge. Inhibition (%) of bronchoconstriction was determined as follows: Inhibition (%) = (1.0% - maximum bronchoconstriction in test/% maximum bronchoconstriction in control) x 100. The maximum bronchoconstriction was obtained within 20 min after the EA challenge and its control value was 73 ± 9% (mean ± S.D., n=4). The number of test animals was 2 and the mean inhibition was compared with that of FPL-55712 (Fisons Limited) of the following formula:



Effect of the test compounds (2 mg/kg, i.v.) are shown in Table 4-(1) and 4-(2).

Table 4-(1)

Test compound No.	Inhibition (%)	Test compound No.	Inhibition (%)
2	21	52	30
9	35	43	14
10	31	13	43
11	21	15	56
14	28	53	38
22	23		
44	72	FPL-55712 (Reference compound)	27

In the Table, the dose of EA was 10 mg/kg, and each compound was dissolved or suspended in 3% Tween 80.

Table 4-(2)

Test compound (%)	Solution or suspension for test compound	Inhibition (%)
74	Tween 80	31
75	Tween 80	57
79	Tween 80	61
86	Tween 80	29
87	Tween 80	61
88	Tween 80	45
89	PEG*	79
91	PEG	73
97	Tween 80	32
103	Tween 80	76
105	Tween 80	29
106	Tween 80	65
109	Tween 80	30
112	Tween 80	49
119	Tween 80	33
EPL-55712	Tween 80	60

In the Table, the dose of EA was 0.1 mg/kg.
*: PEG represents polyethylene glycol-400.

(iv) Effect on bronchoconstriction induced by intravenous (i.v.) administration of LTD_4

Bronchoconstrictions induced by i.v. administration of LTD_4 in guinea-pigs (350-450 g) were measured as described in anaphylactic bronchoconstriction. Guinea-pigs were anaesthetized with urethane (1.5 g/kg) and the trachea was cannulated to record total pulmonary resistance. The right jugular vein was cannulated for the administration of the all agents. The guinea-pigs were artificially ventilated by a small respirator set at a stroke volume of 5 ml and a rate of 50 breaths per min. LTD_4 (2 μg/kg)-induced bronchoconstriction was shown by the increase in air overflow volume. After the response to histamine (5 μg/kg) was checked, the first response to LTD_4 was obtained as control. Test compounds, 2 mg/kg in 3% Tween 80, were administered 2 min prior to the second response to LTD_4, because there was no difference between the first response and the second response to LTD_4. Inhibition (%) of the bronchoconstriction was determined as follows: Inhibition (%) = (1.0 - peak value in the second response/peak value in the first response) x 100. Results in all of the experiments were compared with those of FPL-55712 (Fisons Limited).

Effect of the test compounds (2 mg/kg, i.v.) are shown in Table 5.

Table 5

Test compound No.	Inhibition (%)
1	23
3	60.6
9	38
44	72.5
FPL-55712	100

B. Acute toxicity test

(i) Test method-(1)

The lethal ratio was determined in ddY strain male mice (4 weeks old) at 7 days after the oral administration of test compounds. The results are shown in Table 6.

Table 6

Dose (300 mg/kg, P.O.)	
Test compound No.	Lethal ratio
10	0/3
4	0/3

(ii) Test method-(2)

The lethal ratio was determined in ddY strain male mice (4 weeks old) at 7 days after the intraperitoneal injection of test compounds. The results are shown in Table 7.

Table 7

Test compound No.	Dose (mg/kg)	Lethal ratio (Death number/Experimental number)
75	100	0/2
76	200 400	0/2 0/1
77	200 400	0/2 0/2
78	200 400	0/2 0/1
79	200	0/2
80	200 400	0/2 0/1
86	200 400	0/2 0/1
87	200 400	0/2 0/2
88	200 400	0/2 0/2
89	200 400	0/2 0/1
90	200 400	0/2 0/2
91	100	0/2
94	200	0/2
97	200 400	0/2 0/1
99	100	0/2
102	100	0/2
103	200	0/2
105	100	0/2
106	200 400	0/2 0/1

From these results, it is evident that the compounds of the present invention produce prominent effects on the angtagonism for SRS-A and its major constituents LTC_4 and LTD_4 in vitro and in vivo. Therefore, the compounds of the present invention are proved to be useful for prophylactic and therapeutic drugs in SRS-A-induced various allergic diseases, for example bronchial asthma, allergic rhinitics and urticaria.

As the manner of administration of the compounds of the present invention, there may be mentioned a non-oral administration by injection (subcutaneous, intravenous, intramuscular or intraperitoneal injection), an ointment, a suppository or an aerosol, or an oral administration in the form of tablets, capsules, granules, pills, sirups, liquids, emulsions or suspensions.

The above pharmacological or veterinary composition contains a compound of the present invention in an amount of from about 0.1 to about 99.5% by weight, preferably from about 0.5 to about 95% by weight, based on the total weight of the composition. To the compound of the present invention or to the composition containing the compound of the present invention, other pharmacologically or veterinarily active compounds may be incorporated. Further, the composition of the present invention may contain a plurality of compounds of the present invention.

The clinical dose of the compound of the present invention varies depending upon the age, the body weight, the sensitivity or the symptom, etc. of the patient. However, the effective daily dose is usually from 0.003 to 1.5 g, preferably from 0.01 to 0.6 g, for an adult. However, if necessary, an amount outside the above range may be employed.

The compounds of the present invention may be formulated into various suitable formulations depending upon the manner of administration, in accordance with conventional methods commonly employed for the preparation of pharmaceutical formulations.

Namely, tablets, capsules, granules or pills for oral administration, may be prepared by using an excipient such as sugar, lactose, glucose, starch or mannitol; a binder such as sirups, gum arabic, gelatin, sorbitol, tragacant gum, methyl cellulose or polyvinylpyrrolidone; a disintegrant such as starch, carboxymethyl cellulose or its calcium salt, crystal cellulose powder or polyethylene glycol; a gloss agent such as talc, magnesium or calcium stearate or colloidal silica; or a lubricant such as sodium laurate or glycerol. The injections, solutions, emulsions, suspensions, sirups or aerosols, may be prepared by using a solvent for the active ingredient such as water, ethyl alcohol, isopropyl alcohol, propylene glycole, 1,3-butylene glycol, or polyethylene glycol; a surfactant such as a sorbitol

fatty acid ester, a polyoxyethylene sorbitol fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene ether of hydrogenated caster oil or lecithin; a suspending agent such as a sodium salt of carboxymethyl, a cellulose derivative such as methyl cellulose, or a natural rubber such as tragacant gum or gum arabic; or a preservative such as a paraoxy benzoic acid ester, benzalkonium chloride or a salt of sorbic acid. Likewise, the suppositories may be prepared by using e.g. polyethylene glycol, lanolin or cocoa butter.

Now, the present invention will be described in detail with reference to Examples. However, it should be understood that the present invention is by no means restricted by these specific Examples. In Examples or in Reference Examples, the symbols "NMR" and "MS" indicate "nuclear magnetic resonance spectrum" and "mass spectrometry". In the NMR data, only the characteristic absorptions are given. Likewise, in the MS data, only the principal peaks or typical fragment peaks are given.

In this specification, "Me" means a methyl group, "Et" an ethyl group, "Pr" a propyl group, "Bu" a butyl group, and "Ph" a phenyl group. Likewise, a "n" indicates "normal", "i" indicates "iso", and "t" indicates "tertiary".

REFERENCE EXAMPLE 1

3,4-Dimethoxybenzylamine hydrochloride

A mixture comprising 24.06 g of 3,4-dimethoxybenzaldehyde, 14.28 g of hydroxylamine sulfate, 7.25 g of sodium hydroxide, 300 ml of methanol and 250 ml of water, was refluxed under stirring for one hour. After cooling, 14.5 g of sodium hydroxide was added and dissolved in the mixture, and then 40 g of Raney nickel (Ni-Al alloy) was gradually added under cooling with ice. After the completion of the addition, the ice bath was removed, and the mixture was continuously stirred at room temperature for one hour. The reaction mixture was filtered, and methanol in the filtrate was distilled off under reduced pressure, and the residue was extracted with diethyl ether. The extract was washed with a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a colorless oily substance.

NMR($CDCl_3$)δ: 6.77 (3H, s), 3.81, 3.80 (each 3H, s), 3.75 (2H, s), 1.58 (2H, s, disappeared upon the addition of D_2O)

The residual oily substance was diluted with 100 ml of diethyl ether, and 25 ml of a 1,4-dioxane solution of 6N HCl was added thereto under cooling with ice. The precipitated solid substance was collected by filtration, and washed with ether to obtain 29.36 g of the above identified compound as a colorless powder.

In a similar manner as above, benzylamines having different substituents, i.e. 4-ethyl, 4-i-propyl, 3-methyl-4-methoxy, 3-methoxy, 4-ethoxy, 4-n-propoxy, 3,4-methylenedioxy, 3-amyloxy-4-methoxy and 4-cyano, and their hydrochlorides were prepared, respectively, from the corresponding benzaldehydes.

REFERENCE EXAMPLE 2

4-Diethylaminobenzylamine hydrochloride

A mixture of 8.80 g of 4-diethylaminobenzaldehyde, 4.59 g of O-methylhydroxylamine hydrochloride, 11.87 g of pyridine and 80 ml of ethanol was refluxed under stirring for one hour. The solvent was distilled off under reduced pressure, and water was added to the residue. The mixture was extracted with benzene. The extract was washed with water (twice) and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain 10.30 g of O-methylaldoxime as a pale yellow oily substance.

NMR($CDCl_3$)δ:7.87 (1H, s), 7.34, 6.54 (each 2H, ABq), 3.85 (3H, s), 3.33 (4H, q), 1.15 (6H, t)

Into a suspension comprising 7.6 g of sodium borohydride and 200 ml of tetrahydrofuran, a solution obtained by dissolving 22.8 g of trifluoroacetic acid in 10 ml of tetrahydrofuran, was dropwise added over a period of 20 minutes under stirring and cooling with ice. After the completion of the dropwise addition, the ice

bath was removed, and the reaction solution was stirred at room temperature for one hour, and then 10.30 g of the above obtained o-methylaldoxime was added thereto. The reaction was conducted at the same temperature for one hour, and then the mixture was refluxed for two hours. After cooling, water was added to the reaction mixture under cooling with ice to decompose the excess reducing agent. Tetrahydrofuran was distilled off, and the residue thereby obtained was extracted with dichloromethane. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off. Then, 25 ml of a dioxane solution of 6N HCl was added to the residue under cooling with ice. The mixture was subjected to distillation under reduced pressure. The solid substance thereby obtained was treated with methanol-ether to obtain 11.13g of the above identified compound as a colorless powder. The NMR spectrum of the free amine is as follows:

NMR($CDCl_3$)δ: 7.06, 6.56 (each 2H, ABq), 3.66 (2H, s), 3.27 (4H, q), 1.55 (2H, s, disappeared upon the addition of D_2O), 1.11 (6H, t)

In the same manner as above, benzylamines having various substituents, i.e. 4-morpholino and 4-methylmercapto, and their hydrochlorides, were prepared, respectively, from the corresponding benzaldehydes.

REFERENCE EXAMPLE 3

4-(2-Carboxy-trans-ethenyl)benzylamine

Into a mixture of 0.946 g of sodium borohydride and 100 ml of tetrahydrofuran, a mixed solution of 2.850 g of trifluoroacetic acid and 20 ml of tetrahydrofuran, was dropwise added under stirring and cooling with ice. After the completion of the dropwise addition, the ice bath was removed, and the reaction mixture was stirred for one hour. Then, a solution obtained by dissolving 4.325 g of 4-cyanociannamic acid obtained by heating and condensing 4-cyanobenzaldehyde with malonic acid in pyridine in the presence of a catalytic amount of piperidine, in 140 ml of tetrahydrofuran and 30 ml of 1,4-dioxane, was dropwise added to the reaction mixture, and stirred at room temperature for 2.5 hours. After cooling, ice pieces were added to decompose the excess reducing agent. Then, the reaction mixture was concentrated, and the precipitated powder was collected by filtration and subjected to vacuum drying to obtain 3.50 g of the above identified compound as a colorless powder.

REFERENCE EXAMPLE 4

4-Chlorobenzylamine hydrochloride

Into a mixture comprising 7.30 g of sodium borohydride, 6.00 g of 4-chlorobenzamide and 100 ml of 1,4-dioxane, a mixed solution of 11.58 g of acetic acid and 30 ml of 1,4-dioxane, was dropwise added under

stirring and cooling with ice over a period of 30 minutes. After the dropwise addition, the reaction mixture was refluxed under stirring for two hours. After cooling, ice pieces were gradually added to decompose the excess reducing agent, and the solvent was distilled off under reduced pressure. Then, the residue was extracted with chloroform. The extract was washed with a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to a concentration of about 80 ml. The concentrated solution was cooled with ice, and 10 ml of a dioxane solution of 6N HCl was dropwise added thereto. The precipitated solid substance was treated with methanol-ether to obtain 3.16 g of the above identified compound as a colorless powder. The NMR spectrum of the free amine is as follows:

NMR($CDCl_3$)δ: 7.38 (4H, s), 4.16 (2H, s), 1.55 (2H, s, disappeared upon the addition of D_2O)

REFERENCE EXAMPLE 5

4-Dimethylaminocarbonylbenzylamine hydrochloride

Into a mixture comprising 7 g of 4-carboxy-N-t-butoxycarbonylbenzylamine obtained by reacting 4-amino-methylbenzoic acid with di-t-butyl dicarbonate in the presence of sodium hydroxide in a usual manner, 6.36 g of triethylamine and 150 ml of dichloromethane, 4.14 g of ethyl chloroformate was gradually added under stirring and cooling with ice. After the completion of the

dropwise addition, the mixture was stirred under cooling with ice for one hour, and 2.51 g of dimethylamine hydrochloride was added thereto at the same temperature. The ice bath was removed, and the reaction solution was stirred at room temperature for 30 minutes. The reaction solution was washed successively with an aqueous sodium hydrogencarbonate solution, water, a 10% citric acid aqueous solution and water, and dried over sodium sulfate, and then the solvent was distilled off. The residue thereby obtained was subjected to silica gel column chromatography (developer; $CHCl_3$:MeOH = 19:1, v/v) to obtain 3.22 g of 4-dimethylaminocarbonyl-N-t-butoxycarbonylbenzylamine as a yellow oily substance.

NMR($CDCl_3$)δ: 7.28 (4H, s), 4.28 (2H, d), 3.01 (6H, s) 1.44 (9H, s)

3.22 g of the above obtained 4-dimethylaminocarbonyl-N-t-butoxycarbonylbenzylamine was dissolved in 5 ml of methanol, and 10 ml of a dioxane solution of 6N HCl was added thereto, and then the mixture was left to stand still overnight. The mixture was subjected to distillation under reduced pressure. The solid substance thereby obtained was treated with methanol-ether to obtain 2.6 g of the above identified compound as a colorless powder. The NMR spectrum of the free amine is as follows:

NMR($CDCl_3$)δ: 7.31 (4H, s), 3.82 (2H, s), 3.00 (6H, s), 1.63 (2H, s)

In a similar manner as above, benzylamines having different substituents, i.e. 4-diethylaminocarbonyl, 4-di-n-propylaminocarbonyl, 4-(4-methylpiperazinylcarbonyl), 4-(4-ethylpiperazinylcarbonyl) and 4-morpholinocarbonyl, and their hydrochlorides were prepared, respectively, from the corresponding 4-aminomethylbenzoic acids.

REFERENCE EXAMPLE 6

4-Dimethylaminomethylbenzylamine

Into a suspension of 0.95 g of lithium aluminum hydride and 100 ml of tetrahydrofuran, a solution obtained by dissolving 1.77 g of 4-dimethylaminocarbonylbenzylamine prepared in Reference Example 5 in 50 ml of tetrahydrofuran, was dropwise added under stirring, and the reaction solution was refluxed for 3 hours. After cooling, the reaction solution was cooled with ice, and ice pieces were gradually added to decompose the excessive reducing agent. Tetrahydrofuran was distilled off, and the residue thereby obtained was extracted with dichloromethane. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain 1.13 g of the above identified compound as a pale yellow oily substance.

NMR($CDCl_3$)δ: 7.23 (4H, s), 3.82 (2H, s), 3.39 (2H, s), 2.21 (6H, s), 1.51 (2H, s, disappeared upon the addition of D_2O)

In a similar manner as above, benzylamines having different substituents, i.e. 4-diethylaminomethyl, 4-(4-methylpiperazinylmethyl), 4-(4-ethylpiperazinylmethyl) and 4-morpholinomethyl were prepared, respectively, from the corresponding benzylamines prepared in Reference Example 5.

REFERENCE EXAMPLE 7

4-Di-n-propylaminomethyl-N-methylbenzylamine

Into a mixture of 1.31 g of lithium aluminum hydride and 50 ml of tetrahydrofuran, a solution obtained by dissolving 2.88 g of 4-di-n-propylaminocarbonyl-N-t-butoxycarbonylbenzylamine prepared in Reference Example 5 in 70 ml of tetrahydrofuran, was dropwise added under stirring at room temperature. After the completion of the dropwise addition, the mixture was refluxed for 3 hours. After cooling, ice pieces were gradually added to the mixture under cooling with ice to decompose the excessive reducing agent. Tetrahydrofuran was distilled off under reduced pressure, and the residue was extracted with chloroform. The extract was washed with water, and dried over sodium sulfate, and then the solvent was distilled off to obtain 1.30 g of the above identified compound as a pale yellow oily substance.

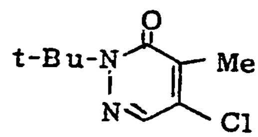
NMR($CDCl_3$)δ: 7.25 (4H, s), 3.71 (2H, s), 3.51 (2H, s), 2.43 (3H, s), 1.86 (6H, t)

In a similar manner as above, 4-methyl-N-methylbenzylamine and 3-methoxy-N-methylbenzylamine were

prepared, respectively, from 4-methyl-N-ethoxycarbonylbenzylamine and 3-methoxy-N-ethoxycarbonylbenzylamine.

REFERENCE EXAMPLE 8

4-Methyl-5-chloro-2-t-butyl-3(2H)pyridazinone



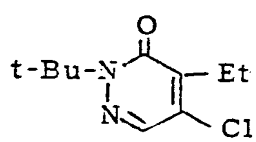
To 7.2 g of metal magnesium in 10 ml of dried ethyl ether, 33.5 g (0.25 mol) of methyl iodide was dropwise added in a nitrogen stream to prepare a Grignard reagent. After the completion of the dropwise addition of methyl iodide, 1000 ml of dried toluene was added to the mixture. The solution was heated to a temperature of from 60 to 70°C, and methyl iodide was further added until magnesium was completely dissolved. The Grignard reagent was cooled to room temperature, and a solution obtained by dissolving 22.1 g (0.1 mol) of 2-t-butyl-4,5-dichloro-3(2H)pyridazinone in 200 ml of dried toluene, was dropwise added over a period of 20 minutes. After the completion of the dropwise addition, the mixture was reacted at room temperature for 1.5 hours, and a mixed solution of 100 ml of concentrated hydrochloric acid and 900 ml of ice water was poured in the reaction solution for liquid separation. Then, the organic layer was washed with 500 ml of 10% sodium

hydroxide and 500 ml of water, and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure to obtain 17. 2 g of a crude product. This crude product was subjected to distillation (boiling point: 60-62°C/0.22 mmHg), and separated and purified by silica gel column chromatography (developer; hexane:acetone = 15:1) to obtain 4.5 g of 2-t-butyl-5-chloro-4-methyl-3(2H)-pyridazinone. $n_D^{20} = 1.5238$

NMR($CDCl_3$)δ: 1.63 (9H, s), 2.23 (3H, s), 2.66 (1H, s),

REFERENCE EXAMPLE 9

4-Ethyl-5-chloro-2-t-butyl-3(2H)pyridazinone



Into a four-necked flask of 1 liter, 43 g of ethylmagnesium bromide (3 mol/liter of an ether solution) and 200 ml of dehydrated toluene were charged. While thoroughly stirring the mixture at room temperature, 22.1 g (0.1 mol) of 2-t-butyl-4,5-dichloro-3(2H)pyridazinone was added in three portions. The reaction temperature was raised to a level of about 60°C, and the stirring was continued for about 30 minutes. The disappearance of the starting dichloropyridazinone was confirmed by thin layer chromatography (developer; hexane:acetone = 20:1, v/v),

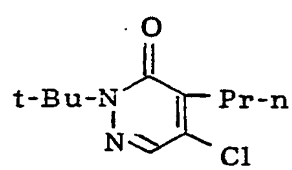
whereupon the reaction was terminated. After the addition of about 300 ml of chilled water, the mixture was stirred vigorously, and transferred to a separating funnel, and then the aqueous layer was removed. The organic layer was washed with about 200 ml of water, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The pale brown oily substance thereby obtained was purified by silica gel column chromatography (developer; benzene) to obtain pale yellow crystals. 1.45 g (yield: 67.6%).

mp: 61.5 - 62.5°C

NMR($CDCl_3$)δ: 7.62 (1H, s), 2.72 (2H, q), 1.61 (9H, s), 1.14 (2H, t)

REFERENCE EXAMPLE 10

4-n-Propyl-5-chloro-2-t-butyl-3(2H)pyridazinone



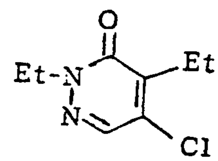
The desired product was obtained in the same manner as in Reference Example 9 except that the starting ethylmagnesium chloride used in Reference Example 9 was replaced by n-propylmagnesium chloride.

NMR($CDCl_3$)δ: 7.64 (1H, s), 2.70 (2H, q), 1.66 (2H, m), 1.62 (9H, s), 0.98 (3H, t)

mp: 45°C

REFERENCE EXAMPLE 11

4-Ethyl-5-chloro-2-ethyl-3(2H)pyridazinone

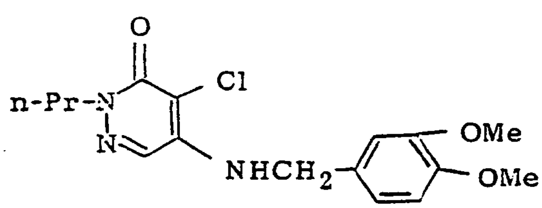


The desired product was obtained as a pale yellow oil in the same manner as in Reference Example 9 except that the starting 2-t-butyl-4,5-dichloro-3(2H)-pyridazinone used in Reference Example 9 was replaced by 2-ethyl-4,5-dichloro-3(2H)pyridazinone.

NMR($CDCl_3$)δ: 7.68 (1H, s), 4.18 (2H, q), 2.75 (2H, q), 1.35 (3H, t)

EXAMPLE 1

4-Chloro-5-(3,4-dimethoxybenzylamino)-2-n-propyl-3-(2H)pyridazinone (Compound No. 14)



A mixture comprising 1.52 g of 3,4-dimethoxybenzylamine hydrochloride prepared in Reference Example 1, 0.62 g of 4,5-dichloro-2-n-propyl-3(2H)pyridazinone, 1.66 g of potassium carbonate, 10 ml of 1,4-dioxane and 30 ml of water was refluxed under stirring for 5 hours. The solvent was distilled off under reduced pressure, and

water was added to the residue thereby obtained, and the mixture was extracted with ethyl acetate. The extract was washed successively with 2% diluted hydrochloric acid, water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale yellow oily substance. This substance was crystallized from diethyl ether-n-hexane to obtain 522 mg of the above identified compound having a melting point of from 139 to 140°C as colorless crystals.

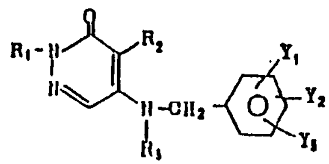
IR (ν_{max}^{KBr}) cm^{-1}: 3300, 1635 (shoulder), 1605, 1525

NMR($CDCl_3$) δ: 7.47 (1H, s), 6.65-6.87 (3H, m), 5.03 (1H, broad s), 4,47, 4.37 (total 2H, each s), 4.04 (2H, t), 3.82 (6H, s), 2.0-1.5 (2H, m), 0.91 (3H, t)

MS (m/e): 337(M^+), 302, 151 (100%)

The compounds as identified in Table 8 were prepared in the synthetic manner and after-treatment similar to those in Example 1 except that the benzylamine hydrochlorides with Y_1, Y_2, Y_3 and R_3 as identified in Table 8 were used instead of the starting 3,4-dimethoxy-benzylamine hydrochloride used in Example 1, and the 4,5-di-(chloro or bromo-)-2-alkyl3(2H)pyridazinones with R_1 and R_2 as identified in Table 8 were used instead of the starting 4,5-dichloro-2-n-propyl-3(2H)pyridazinone. In the NMR data, only the characteristic absorptions are given in Table 8.

Table 8

Synthesis of 

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(°C)	NMR ($CDCl_3$) δ	MS (m/e)
1	t-Bu	Cl	H	H	H	H	151.5 - 152.5	7.51(1H, s), 4.60, 4.50(total 2H, each s), 1.61(9H, s)	
2	t-Bu	Cl	H	3-Me	H	H	155	7.40(1H, s), 4.51, 4.41(total 2H, each s), 2.36(3H, s), 1.61(9H, s)	
3	t-Bu	Cl	H	4-Me	H	H	169.5 - 171.5	7.50(1H, s), 4.51, 4.41(total 2H, each s), 2.36(3H, s), 1.60(9H, s)	
4	t-Bu	Cl	H	4-Et	H	H	138	7.51(1H, s), 4.51, 4.41(total 2H, each s), 1.61(9H, s), 1.22(3H, t)	
5	t-Bu	Cl	H	4-i-Pr	H	H	148	7.45(1H, s), 4.48, 4.38(total 2H, each s), 1.61(9H, s), 1.23(6H, d)	
6	Et	Cl	H	3-OMe	H	H	120	7.57(1H, s), 4.58, 4.48(total 2H, each s), 3.81(3H, s), 1.34(3H, t)	293(M^+), 121(100%)
7	i-Pr	Cl	H	3-OMe	H	H	148 - 150	7.56(1H, s), 4.54, 4.45(total 2H, each s), 3.79(3H, s), 1.29(6H, d)	307(M^+), 121(100%)
8	t-Bu	Cl	H	3-OMe	H	H	180 - 182	7.47(1H, s), 4.54, 4.44(total 2H, each s), 3.79(3H, s), 1.61(9H, s)	321(M^+), 121(100%)
9	t-Bu	Cl	H	4-OMe	H	H	141 - 142	7.52(1H, s), 4.51, 4.41(total 2H, each s), 3.80(3H, s), 1.61(9H, s)	
10	t-Bu	Cl	H	4-OEt	H	H	124	7.42(1H, s), 4.42, 4.32(total 2H, each s), 1.60(9H, s), 1.30(3H, t)	

Table 8 (cont'd)

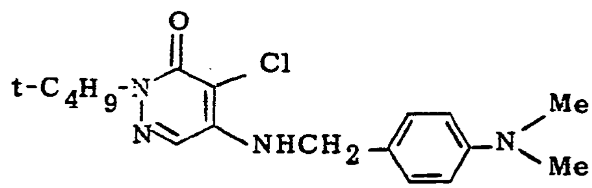
Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	NMR ($CDCl_3$) δ	MS (m/e)
11	t-Bu	Cl	H	4-O-Pr-n	H	H	129-132	7.51(1H, s), 4.49, 4.39(total 2H, each s), 1.61(9H, s), 1.02(3H, t)	
12	t-Bu	Cl	H	3-Me	4-OMe	H	168-170	7.47(1H, s), 4.43, 4.33(total 2H, each s), 3.79(3H, s), 2.20(3H, s), 1.60(9H, s)	
13	Et	Cl	H	3-OMe	4-OMe	H	116-117	7.48(1H, s), 4.47, 4.30(total 2H, each s), 3.83(6H, s), 1.32(3H, t)	323(M^+), 151(100%)
15	i-Pr	Cl	H	3-OMe	4-OMe	H	118-119	7.51(1H, s), 4.47, 4.37(total 2H, each s), 3.81(6H, s), 1.24(6H, d)	337(M^+), 151(100%)
16	t-Bu	Cl	H	3-OMe	4-OMe	H	156-157	7.44(1H, s), 4.46, 4.36(total 2H, each s), 3.84(6H, s), 1.60(9H, s)	
17	t-Bu	Br	H	3-OMe	4-OMe	H	173-175	7.37(1H, s), 4.47, 4.38(total 2H, each s), 3.85(6H, s), 1.60(9H, s)	395(M^+), 151(100%)
18	t-Bu	Cl	H	3-O> 4-O		H	162-164	7.39(1H, s), 5.89(2H, s), 4.41, 4.31 (total 2H, each s), 1.60(9H, s)	335(M^+), 135(100%)
19	Et	Cl	H	3-O-C_5H_{11}-n	4-OMe	H	113	7.57(1H, s), 4.49, 4.39(total 2H, each s), 3.87(3H, s)	378(M^+), 207(100%)
20	t-Bu	Cl	H	3-O-C_5H_{11}-n	4-OMe	H	117	7.50(1H, s), 4.46, 4.36(total 2H, each s), 3.83(3H, s), 1.61(9H, s)	407(M^+), 207(100%)
21	t-Bu	Cl	H	4-SMe	H	H	171-171.5	7.49(1H, s), 4.49, 4.39(total 2H, each s), 2.45(3H, s), 1.59(9H, s)	337(M^+), 137(100%)
22	t-Bu	Cl	H	4-Cl	H	H	152.5-153	7.45(1H, s), 4.51, 4.41(total 2H, each s), 1.59(9H, s)	325(M^+), 125(100%)

Table 8 (cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^{o}C)	NMR ($CDCl_3$) δ	MS (m/e)
23	t-Bu	Cl	H	4-CO_2H	H	H	239-241	($CDCl_3$+DMSO-d_6):7.37(1H, s), 4.65, 4.55(total 2H, each s), 1.57(9H, s)	335(M^+), 135(100%)
24	t-Bu	Cl	H	4-CH=CH-CO_2H	H	H	259-261	($CDCl_3$+DMSO-d_6): 7.45, 6.36(each 1H, ABq, J=16Hz), 4.55, 4.44 (total 2H, each s), 1.49(9H, s)	361(M^+), 161(100%)
63	i-Pr	Cl	H	4-CO_2H	H	H	238-240	($CDCl_3$+DMSO-d_6):7.94, 7.33(each 2H, ABq), 4.65, 4.55(total 2H, each s), 1.26(6H, d)	321(M^+), 135(100%)
72	t-Bu	Cl	H	4-CN	H	H	135.5-136	7.63, 7.42(each 2H, ABq), 7.30(1H, s), 4.65, 4.55(total 2H, each s), 1.58(9H, s)	316(M^+), 116(100%)

EXAMPLE 2

4-Chloro-5-(4-dimethylaminobenzylamino)-2-t-butyl-3(2H)-pyridazinone (Compound No. 25)



A mixture comprising 2.81 g of 4-dimethylaminobenzylamine dihydrochloride, 1.55 g of 4,5-dichloro-2-t-butyl-3(2H)pyridazinone, 3.87 g of potassium carbonate, 30 ml of 1,4-dioxane and 10 ml of water was refluxed under stirring for 15 hours. The solvent was distilled off under reduced pressure, and water was added to the residue thereby obtained, and the mixture was extracted with benzene. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale yellow solid substance. This substance was subjected to silica gel column chromatography, and eluted with benzene-ethyl acetate (5:1, v/v). The colorless solid substance thereby obtained was crystallized from benzene-n-hexane to obtain 1.20 g of the above identified compound having a melting point of from 168 to 169°C as colorless crystals.

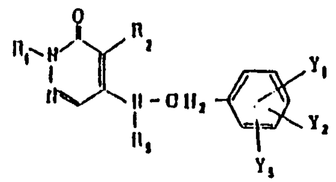
IR (ν_{max}^{KBr}) cm^{-1}: 3300, 1630 (shoulder), 1600, 1520

NMR($CDCl_3$)δ: 7.46 (1H, s), 7.09, 6.63 (each 2H, ABq), 4.85 (1H, broad s), 4.38, 4.29 (total 2H, each s), 2.90 (6H, s), 1.60 (9H, s)

MS (m/e): 334(M^+), 299, 243, 134 (100%)

The compounds as identified in Table 9 were prepared in the synthetic manner and after-treatment similar to those in Example 2 except that the benzylamine dihydrochlorides with Y_1, Y_2, Y_3 and R_3 as identified in Table 9 were used instead of the starting 4-dimethylaminobenzylamine dihydrochloride used in Example 2, and the 4,5-di(chloro or bromo)-2-alkyl-3(2H)pyridazinones with R_1 and R_2 as identified in Table 8 were used instead of the starting 4,5-dichloro-2-t-butyl-3(2H)pyridazinone. In the NMR data, only the characteristic absorptions are given in Table 9.

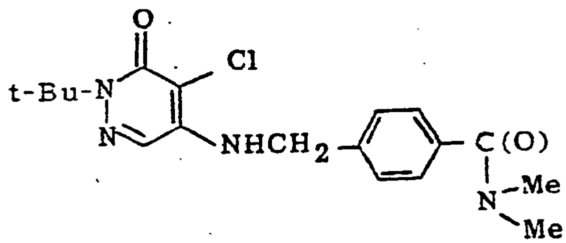
Table 9 Synthesis of



Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(°C)	NMR ($CDCl_3$) δ	MS (m/e)
26	i-Pr	Cl	H	4-N(Me)$_2$	H	H	161-162.5	7.59(1H, d), 4.41, 4.31(total 2H, each s), 2.91(6H, s), 1.29(6H, d)	320(M$^+$), 134(100%)
27	Et	Cl	H	4-N(Me)$_2$	H	H	143.5-144	7.51(1H, s), 4.40, 4.30(total 2H, each s), 2.90(6H, s), 1.31(3H, t)	306(M$^+$), 134(100%)
28	t-Bu	Br	H	4-N(Me)$_2$	H	H	155-156	7.40(1H, s), 4.40, 4.30(total 2H, each s), 2.91(6H, s), 1.60(9H, s)	378(M$^+$), 134(100%)
29	t-Bu	Cl	H	4-N(Et)$_2$	H	H	133.5-134	7.49(1H, s), 4.37, 4.27(total 2H, each s), 1.60(9H, s), 1.15(3H, t)	362(M$^+$), 162(100%)
30	t-Bu	Cl	H	4-N◯O	H	H	163-164	7.42(1H, d), 4.42, 4.32(total 2H, each s), 1.59(9H, s)	376(M$^+$), 176(100%)
31	t-Bu	Cl	H	4-CH$_2$N(Me)$_2$	H	H	Viscous oily substance	7.48(1H, s), 4.56, 4.46(total 2H, each s), 2.35(6H, s), 1.61(9H, s)	340(M$^+$), 249(100%)
32	t-Bu	Cl	H	4-CH$_2$N(Et)$_2$	H	H	Viscous oily substance	7.49(1H, s), 4.56, 4.46(total 2H, each s), 1.60(9H, s), 1.07(6H, t)	376(M$^+$), 361
33	t-Bu	Cl	H	4-CH$_2$N◯O	H	H	135	7.46(1H, s), 4.53, 4.43(total 2H, each s), 3.47(2H, s), 1.59(9H, s)	390(M$^+$), 249(100%)
34	t-Bu	Cl	H	4-CH$_2$N◯NMe	H	H	Viscous oily substance	7.49(1H, s), 4.54, 4.44(total 2H, each s), 2.47(8H, s), 2.30(3H, s), 1.61(9H, s)	403(M$^+$), 202(100%)
35	t-Bu	Cl	H	4-CH$_2$N◯NEt	H	H	Viscous oily substance	7.49(1H, s), 4.57, 4.47(total 2H, each s), 2.48 (8H, s), 1.60 (9H, s), 1.08 (3H, t)	417(M$^+$), 216(100%)

EXAMPLE 3

4-Chloro-5-(4-dimethylaminocarbonylbenzylamino)-2-t-butyl-3(2H)pyridazinone (Compound No. 37)



0.65 g of 4,5-dichloro-2-t-butyl-3(2H)pyridazinone, 1.04 g of 4-dimethylaminocarbonylbenzylamine prepared in Reference Example 5, 0.28 g of pyridine, 20 ml of water and 10 ml of 1,4-dioxane were refluxed under stirring for 15 hours. 1,4-dioxane was distilled off under reduced pressure, and the residue was extracted with chloroform. The extract was washed with diluted hydrochloric acid and water, and dried over sodium sulfate, and then the solvent was distilled off. The residue was treated with n-hexane to obtain 480 mg of the above identified compound having a melting point of from 167 to 169°C as pale yellow crystals.

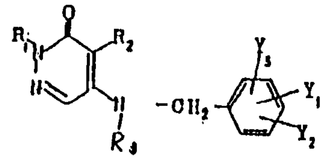
NMR($CDCl_3$) δ: 7.43 (1H, s), 7.40 (4H, s), 5.23 (1H, broad s), 4.61, 4.51 (total 2H, each s), 3.04 (6H, s), 1.62 (9H, s)

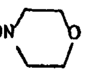
MS (m/e): 362(M^+, 100%)

The compounds as identified in Table 10 were prepared in the synthetic manner and after-treatment similar to those in Example 3 except that the benzylamines with Y_1, Y_2, Y_3 and R_3 as identified in Table 10 were used instead

of the starting 4-dimethylaminocarbonylbenzylamine used in Example 3. In the NMR data, only the characteristic absorptions are shown in Table 10.

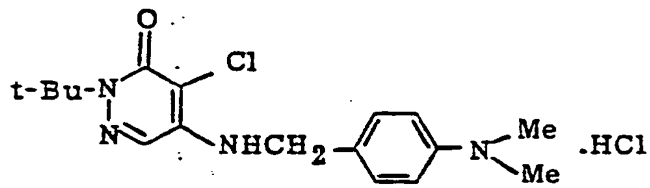
Table 10

Synthesis of 

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(°C)	NMR ($CDCl_3$) δ	MS (m/e)
38	t-Bu	Cl	H	4-CON(Et)$_2$	H	H	Viscous oily substance	7.43(1H, s), 4.60, 4.50(total 2H, each s), 1.60(9H, s), 1.19(6H, s)	390(M^+), 263(100%)
39	t-Bu	Cl	H	4-CON(n-Pr)$_2$	H	H	Viscous oily substance	7.40(1H, s), 4.57, 4.46(total 2H, each s), 1.60(6H, s), 0.85 (6H, t)	418(M^+), 262(100%)
40	t-Bu	Cl	H	4-CONO	H	H	85	7.41(1H, s), 4.61, 4.51(total 2H, each s), 1.60(9H, s)	404(M^+), 235(100%)
41	t-Bu	Cl	H	4-CONNMe	H	H	Viscous oily substance	7.51(1H, s), 4.61, 4.51(total 2H, each s), 2.31(3H, s), 1.60(9H, s)	417(M^+;100%)
42	t-Bu	Cl	H	4-CONNEt	H	H	Viscous oily substance	7.42(1H, s), 4.61, 4.51(total 2H, each s), 1.69(9H, s), 1.59(3H, t)	431(M^+;100%)
71	t-Bu	Cl	H	4-CONH$_2$	H	H	256-258	($CDCl_3$+DMSO-d_6)7.92, 7.40(each 2H, ABq), 7.48(1H, s), 4.57, 4.47(total 2H, each s), 1.55(9H, s)	

EXAMPLE 4

4-Chloro-5-(4-dimethvlaminobenzylamino)-2-t-butyl-3-(2H)pyridazinone hydrochloride (Compound No. 44)

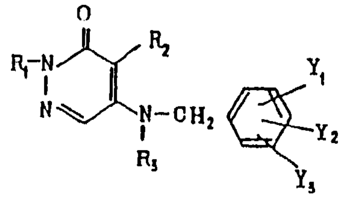


334 ml of 4-chloro-5-(4-dimethylaminobenzylamino)-2-t-butyl-3(2H)pyridazinone (Compound No. 25) prepared in Example 2 was dissolved in a mixed solution of 2 ml of methanol and 2 ml of chloroform. 1.5 ml of a 1,4-dioxane solution of 6N HCl was added to the mixture, and left to stand for 5 minutes while shaking the mixture frequently. The solvent was distilled off under reduced pressure, and the colorless oily substance thereby obtained was dissolved in 15 ml of water and filtrated. The filtrate was subjected to freeze drying, and then to vacuum drying over a solid of sodium hydroxide to obtain 380 mg of the above identified compound as a hygroscopic pale yellow powder.

MS (m/e): 334(M^+-HCl, 100%)

In a similar manner as above, the compounds as identified in Table 11 were obtained.

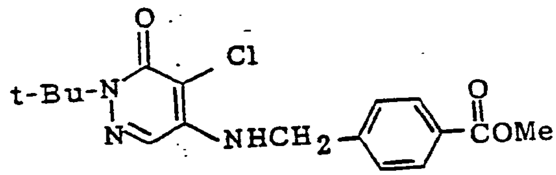
Table 11

Synthesis of  · HCℓ

Compound No.	R_1	R_2	R_3	Y_1	Y_2, Y_3	Properties	MS (m/e)
45	i-Pr	Cl	H	4-$N(Me)_2$·HCl	H	Hygroscopic powder	
46	Et	Cl	H	4-$N(Me)_2$·HCl	H	Hygroscopic powder	
47	t-Bu	Br	H	4-$N(Me)_2$·HCl	H	Hygroscopic powder	
48	t-Bu	Cl	H	4-$CH_2N(Me)_2$·HCl	H	Hygroscopic powder	348(M^+-HCl;100%)
49	t-Bu	Cl	H	4-CH_2N NEt·2HCl	H	Hygroscopic powder	417(M^+-2HCl;100%)
50	t-Bu	Cl	H	4-$CONH(CH_2)_2N(Me)_2$ ·HCl	H	Hygroscopic powder	370(M^+-HCl-Cl)
66	t-Bu	Cl	Me	4-NMe_2·HCl	H	Hygroscopic powder	387, 159(100%)
70	Et	Cl	Me	4-NMe_2·HCl	H	Hygroscopic powder	302 159 134(100%)

EXAMPLE 5

4-Chloro-5-(4-methoxycarbonylbenzylamino)-2-t-butyl-3-(2H)pyridazinone (Compound No. 51)



Into a mixture comprising 500 mg of 4-chloro-5-(4-carboxybenzylamino)-2-t-butyl-3(2H)pyridazinone (Compound No. 23) prepared in Example 1, 310 mg of potassium carbonate, 10 ml of acetone and 30 ml of water, 230 mg of dimethyl sulfate was dropwise added under stirring and cooling with ice. After the dropwise addition, the mixture was stirred at the same temperature for 1 hour and at room temperature for further 12 hours. The precipitated crystals were collected by filtration, dissolved in chloroform, washed with an aqueous sodium hydrogencarbonate solution, and dried over sodium salfate, and then, the solvent was distilled off. The residue thereby obtained was crystallized from ether-hexane to obtain 60 mg of the above identified compound having a melting point of 153°C as colorless crystals.

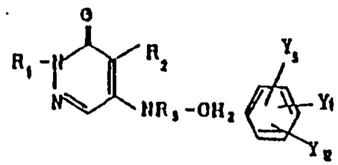
IR (ν_{max}^{KBr}) cm^{-1}: 3310, 1725, 1635 (shoulder), 1605

NMR($CDCl_3$)δ: 8.04, 7.36 (each 2H, ABq), 7.40 (1H, s), 5.45 (1H, broad s), 4.65, 4.55 (total 2H, each s), 3.89 (3H, s), 1.59 (9H, S)

MS (m/e): 349(M^+), 149 (100%)

The compounds as identified in Table 12 were prepared in the synthetic manner and after-treatment similar to those in Example 5 except that the carboxylic acids with Y_1, Y_2, Y_3, R_1, R_2 and R_3 as identified in Table 12 were used instead of the starting 4-chloro-5-(4-carboxybenzylamino)-2-t-butyl-3(2H)pyridazinone used in Example 5. For the preparation of Compound No. 52, diethyl sulfate was used as an esterifying agent. In the NMR data, only the characteristic absorptions are given in Table 12.

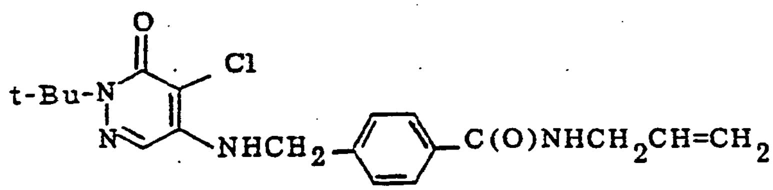
Table 12.

Synthesis of 

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	NMR ($CDCl_3$) δ	MS (m/e)
52	t-Bu	Cl	H	4-CO_2Et	H	H	164-166	7.35(1H, s), 4.61, 4.51(total 2H, each s), 1.60(9H, s), 1.38(3H, t)	363(M^+), 163(100%)
53	t-Bu	Cl	H	4-CH=CH-CO_2Me	H	H	161-163	7.61, 6.36(each 1H, ABq, J=16Hz), 7.36(1H, s), 4.56. 4.46(total 2H, each s), 3.76(3H, s), 1.58(9H, s)	375(M^+), 175(100%)
62	i-Pr	Cl	H	4-CO_2Me	H	H	153.5-154.5	7.43(1H, s), 4.62, 4.52(total 2H, each s), 3.87(3H, s), 1.28(6H, d)	335(M^+), 149(100%)

EXAMPLE 6

4-Chloro-5-(4-allylaminocarbonylbenzylamino)-2-t-butyl-3(2H)pyridazinone (Compound No. 54)



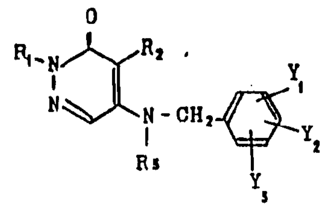
Into a mixture comprising 336 mg of 4-chloro-5-(4-carboxybenzylamino)-2-t-butyl-3(2H)pyridazinone (Compound No. 23) prepared in Example 1 and 5 ml of dimethylformamide, 194 mg of N,N'-carbonyldiimidazole was added under cooling with ice. The mixture was stirred at the same temperature for 1 hour. After the addition of a solution obtained by dissolving 74 mg of allylamine in 2 ml of DMF, the mixture was stirred at the same temperature for 30 minutes, and at room temperature for further 4.5 hours. The solvent was distilled off. The residue thereby obtained was extracted with ethyl acetate. The extract was washed successively with diluted hydrochloric acid, water, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, and dried over sodium salfate, and then the solvent was distilled off to obtain a colorless solid substance. This substance was crystallized from ethyl acetate-ether to obtain 210 mg of the above identified compound having a melting point of from 212 to 213.5°C as colorless crystals.

NMR($CDCl_3$ + DMSO-d_6)δ: 7.75, 7.25 (each 2H, ABq), 7.32 (1H, s), 4.54, 4.44 (total 2H, each s), 1.56 (9H, s)

MS (m/e): 374(M^+), 318, 173 (100%), 118

The compounds as identified in Table 13 were prepared in the synthetic manner and after-treatment similar to those in Example 6 except that the carboxylic acids with R_1, R_2, R_3, Y_1, Y_2 and Y_3 as identified in Table 13 were used instead of the starting 4-chloro-5-(4-carboxybenzylamino)-2-t-butyl-3(2H)pyridazinone used in Example 6, and the amines with Y_1, Y_2 and Y_3 as identified in Table 13 were used instead of the starting allylamine. In the NMR data, only the characteristic absorptions are given in Table 13.

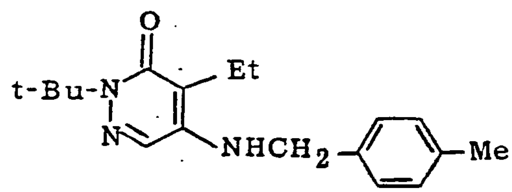
Table 13

Synthesis of 

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^{o}C)	NMR ($CDCl_3$) δ	MS (m/e)
55	t-Bu	Cl	H	4-CONH$(CH_2)_2$OMe	H	H	199.5-200.5	7.35(1H, s), 4.60, 4.50(total 2H, each s), 3.34(3H, s), 1.59(9H, s)	392(M^+), 262(100%)
56	t-Bu	Cl	H	4-CONH$(CH_2)_2$OEt	H	H	165	7.39(1H, s), 4.62, 4.51(total 2H, each s), 1.61(9H, s), 1.24(3H, s)	406(M^+), 262(100%)
57	t-Bu	Cl	H	4-CONH$(CH_2)_3$OEt	H	H	204	7.40(1H, s), 4.61, 4.51(total 2H, each s), 1.60(9H, s), 1.22(3H, t)	420(M^+), 335(100%)
58	t-Bu	Cl	H	4-CONH$(CH_2)_2$N$(Me)_2$	H	H	216-218	7.35(1H, s), 4.61, 4.51(total 2H, each s), 2.24(6H, s), 1.60(9H, s)	405(M^+), 359
59	t-Bu	Cl	H	4-CONH$(CH_2)_3$N$(Me)_2$	H	H	203	7.39(1H, s), 4.60, 4.50(total 2H, each s), 2.36(6H, s), 1.60(9H, s)	419(M^+)
60	t-Bu	Cl	H		H	H	163-166	7.38(1H, s), 6.34(1H, d, J=16Hz), 4.55, 4.45(total 2H, each s), 1.59 (9H, s), 1.27(3H, t)	460(M^+), 260(100%)

EXAMPLE 7

4-Ethyl-5-(4-methylbenzylamino)-2-t-butyl-3(2H)-pyridazinone (Compound No. 36)



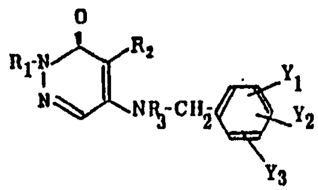
A mixture comprising 260 mg of 4-ethyl-5-chloro-2-t-butyl-3(2H)pyridazinone, 439 mg of 4-methylbenzylamine, 250 mg of potassium carbonate, 4 ml of dimethyl sulfoxide and 0.5 ml of water was stirred at 160°C for 20 hours. After cooling, 20 ml of 2% diluted hydrochloric acid was poured into the reaction mixture under cooling with ice, and the mixture was extracted with benzene. The extract was washed with water (twice) and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale yellow oily substance. The residue was subjected to silica gel column chromatography, and eluted with benzene-ethyl acetate (4:1, v/v). The pale yellow solid substance thereby obtained was crystallized from n-hexane to obtain 57 mg of pale yellow crystals having a melting point of from 156 to 158°C.

NMR($CDCl_3$)δ: 7.40 (1H, s), 7.09 (4H, s), 4.35 (2H, s), 2.46 (2H, q), 2.31 (3H, s), 1.59 (9H, s), 1.06 (3H, t)

Mass (m/e): 299(M^+), 243 (100%), 105

The compound as identified in Table 14 was prepared in the synthetic manner and after-treatment similar to those in Example 7 except that the 4-alkyl-5-chloro-2-alkyl-3(2H)pyridazinone with R_1 and R_2 as identified in Table 14 was used instead of the starting 4-ethyl-5-chloro-2-t-butyl-3(2H)pyridazinone used in Example 7, and the benzylamine derivative with R_3, Y_1, Y_2 and Y_3 as identified in Table 14 was used instead of the starting 4-methylbenzylamine. In the NMR data, only the characteristic absorptions were given in Table 14.

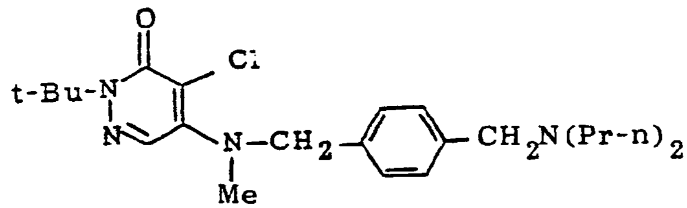
Table 14

Synthesis of 

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	NMR ($CDCl_3$) δ	MS (m/e)
73	t-Bu	Me	H	3-OMe	4-OMe	H	182-183.5	7.44(1H, s), 4.44, 4.34(total 2H, each s), 3.85(6H, s), 1.95(3H, s), 1.60(9H, s)	331 (M^+), 151(100%)

EXAMPLE 8

4-Chloro-5-(4-di-n-propylaminomethyl-N-methylbenzyl-amino)-2-t-butyl-3(2H)pyridazinone (Compound No. 43)



A mixture comprising 0.3 g of 4,5-dichloro-2-t-butyl-3(2H)pyridazinone, 0.65 g of 4-di-n-propylaminomethyl-N-methylbenzylamine prepared in Reference Example 6, 0.19 g of potassium carbonate, 8 ml of 1,4-dioxane and 16 ml of water was stirred under stirring for 8 hours. 1,4-Dioxane was distilled off under reduced pressure, and the residue was extracted with chloroform. Then, the extract was dried over sodium sulfate, and the solvent was distilled off. The residue thereby obtained was purified with silica gel column chromatography by using benzene-ethyl acetate (1:1, v/v) as a developer to obtain 0.15 g of the above identified compound as a viscous oily substance.

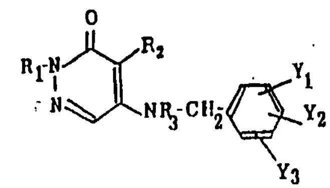
NMR($CDCl_3$) δ: 7.57 (1H, s), 7.28 (4H, s), 4.58 (2H, s), 3.53 (2H, s), 3.01 (3H, s), 2.40 (4H, t), 1.62 (9H, s), 0.86 (3H, t)

MS (m/e): 389(M^+-Et, 100%), 382, 317, 262

The compounds as identified in Table 15 were prepared in the synthetic manner and after-treatment similar to those in Example 8 except that the 4,5-dichloro-2-alkyl-

3(2H)pyridazinones with R_1 and R_2 as identified in Table 15 were used instead of the starting 4,5-dichloro-2-t-butyl-3(2H)pyridazinone used in Example 8, and the N-alkylbenzylamines with R_3, Y_1, Y_2 and Y_3 as identified in Table 15 were used instead of the starting 4-di-n-propylaminomethyl-N-methylbenzylamine. In the NMR data, only the characteristic absorptions are given in Table 15.

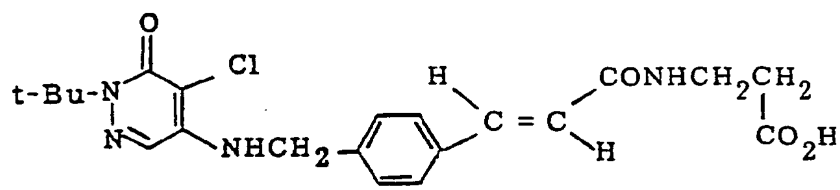
Table 15

Synthesis of 

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	NMR ($CDCl_3$) δ	MS (m/e)
65	t-Bu	Cl	Me	4-NMe_2	H	H	Oily substance	7.55(1H, s), 7.12, 6.66(each 2H, ABq) 4.48 (2H, s) 2.96(3H, s) 2.90(6H, s) 1.62 (9H, s)	313 159 134(100%)
69	Et	Cl	Me	4-NMe_2	H	H	Oily substance	7.58(1H, s), 7.08, 6.63(each 2H, ABq) 4.42 (2H, s) 2.92(3H, s) 2.86(9H, s) 1.31 (3H, t)	285 159 134(100%)
64	t-Bu	Cl	Me	4-Me	H	H	70-71	7.51(1H, s) 7.11(4H, s) 4.52(2H, s) 2.98(3H, s) 2.32(3H, s) 1.61(9H, s)	319(M^+) 263 105(100%)
67	Et	Cl	Me	4-Me	H	H	74	7.53(1H, s) 7.09(4H, s) 4.49(2H, s) 4.10(2H, q) 2.96(3H, s) 2.28(3H, s) 1.28(3H, t)	291(M^+) 256 105(100%)
68	Et	Cl	Me	3-OMe	H	H	Oily substance	7.71(1H, s) 4.67(2H, s) 4.26(2H, q) 3.76(3H, s) 3.03(3H, s) 1.34(3H, t)	307(M^+) 273(100%)

EXAMPLE 9

4-Chloro-5-[4-(β-carboxyethylaminocarbonyl-2-trans-ethenyl)benzylamino]-2-t-butyl-3(2H)pyridazinone (Compound No. 61)



70 mg of the compound prepared in Example 6 (Compound No. 60) was dissolved in 2 ml of MeOH, and 0.2 ml of a 2N sodium hydroxide aqueous solution was added thereto under stirring and cooling with ice, and the mixture was stirred at the same temperature for 1 hour. Diluted hydrochloric acid was added to adjust the pH to a level of about 7, and the reaction mixture was subjected to evaporation under reduced pressure. Diluted hydrochloric acid was poured into the residue thereby obtained, and the mixture was extracted with ethyl acetate. The extract was washed with water (twice) and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale yellow solid substance. This substance was treated with ether to obtain 56 mg of the above identified compound having a melting point of from 170 to 173°C as colorless crystals.

IR (ν_{max}^{KBr}) cm^{-1}: 3260, 1730, 1650 (shoulder), 1605

NMR($CDCl_3$)δ: 7.55, 6.34 (each 1H, ABq, J=16Hz), 7.40 (1H, s), 4.56, 4.46 (total 2H, each s), 1.59 (9H, s)

MS (m/e): 446(M^+)

REFERENCE EXAMPLE 1A

3-n-Propoxy-4-methoxybenzylamine hydrochloride

A mixture comprising 38 g of 3-n-propoxy-4-methoxybenzaldehyde, 19.68 g of hydroxylamine sulfate, 10 g of sodium hydroxide, 250 ml of methanol and 200 ml of water, was refluxed under stirring for 30 minutes. After cooling, 20 g of sodium hydroxide was added and dissolved in the mixture, and then 50g of Raney nickel (Ni-Al alloy) was gradually added under cooling with ice. After the completion of the addition, the ice bath was removed, and the mixture was continuously stirred at room temperature for one hour. The reaction mixture was filtered, and methanol in the filtrate was distilled off under reduced pressure, and then the residue thereby obtained was extracted with benzene. The extract was washed with a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a colorless oily substance.

NMR($CDCl_3$)δ: 6.6-7.0 (3H, m), 3.93 (2H, t), 3.76 (3H, s), 3.73 (2H, s), 2,08-1.71 (2H, m), 1.50 (2H, s), 1.01 (2H, t)

The residual oily substance was diluted with 200 ml of diethyl ether, and 35 ml of a 1,4-dioxane solution of

6N HCl was added thereto under cooling with ice. The precipitated solid substance was collected by filtration, and washed with ether to obtain 33.65 g of the above identified compound as a colorless powder.

In a similar manner as above, benzylamines having different substituents, i.e. 2,4-dimethyl, 4-ethyl, 3-ethyl-4-methoxy, 3-ethoxy, 2-ethoxy, 4-ethoxy, 3-n-propoxy, 3,5-dimethoxy, 2,3-dimethoxy, 3-ethoxy-4-methoxy, 2,5-dimethoxy, 3-n-propoxy-4-methoxy, 3-methoxy-4-ethoxy, 2-ethoxy-4-methoxy and 3,4,5-trimethoxy, and their hydrochlorides were prepared, respectively, from the corresponding benzaldehydes.

REFERENCE EXAMPLE 2A

3-Benzyloxybenzylamine hydrochloride

A mixture comprising 12.72 g of 3-benzyloxybenzaldehyde, 5.76 g of O-methylhydroxylamine hydrochloride, 9.49 g of pyridine and 130 ml of ethanol was refluxed under stirring for 1.5 hours. The solvent was distilled off under reduced pressure, and water was added to the residue. The mixture was extracted with benzene. The extract was washed with water (twice) and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain O-methylaldoxime as pale yellow crystals.

NMR($CDCl_3$) δ: 7.97 (1H, s), 7.33 (5H, s), 7.5-6.8 (4H, m), 5.03 (2H, s), 3.92 (3H, s)

Into a suspension comprising 6.81 g of sodium borohydride and 200 ml of tetrahydrofuran, a solution obtained by dissolving 20.52 g of trifluoroacetic acid in 10 ml of tetrahydrofuran, was dropwise added over a period of 20 minutes under stirring and cooling with ice. After the completion of the dropwise addition, the ice bath was removed, and the reaction solution was stirred at room temperature for one hour, and then a solution obtained by dissolving the above obtained O-methylaldoxime in 50 ml of tetrahydrafuran was added thereto. The reaction was conducted at the same temperature for one hour, and then the mixture was refluxed for two hours. After cooling, ice water was gradually added to the reaction mixture under cooling with ice to decompose the excess reducing agent. Tetrahydrofuran was distilled off, and the residue thereby obtained was extracted with chloroform. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a colorless semi-solid substance. Then, the residue was dissolved in 250 ml of ether, and 10 ml of a dioxane solution of 6N HCl was gradually added thereto under cooling with ice. The mixture was left to stand still overnight. The precipitated solid substance was collected by filtration, and washed with ether, and then dried to obtain 13.52 g of the above identified compound as a colorless powder. The NMR spectrum of the free amine is as follows:

NMR($CDCl_3$)δ: 7.28 (5H, s), 7.3-6.6 (4H, m), 4.96 (2H, s), 3.24 (2H, s), 1.56 (2H, s, disappeared upon the addition of D_2O)

In a similar manner as above, benzylamines having various substituents, i.e. 3-ethyl-4-benzyl, 3-benzyloxy, 4-benzyloxy, 3-ethoxy-4-benzyloxy, 2-benzyloxy-3-ethoxy, 3-n-propoxy-4-benzyloxy, 4-dimethylamino and 4-methylmercapto, and their hydrochlorides, were prepared, respectively, from the corresponding benzaldehydes.

REFERENCE EXAMPLE 3A

4-(1,3-Dioxoranyl)benzylamine

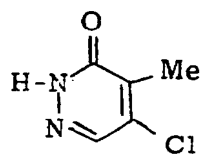
Into a mixture of 3.40 g of sodium borohydride and 200 ml of tetrahydrofuran, a mixed solution of 9.83 g of trifluoroacetic acid and 10 ml of tetrahydrofuran, was dropwise added under stirring and cooling with ice. The ice bath was removed, and the reaction mixture was stirred at room temperature for one hour. Then, 30 ml of a tetrahydrofuran solution containing 13.13 g of 4-cyanobenzaldehyde ethylene acetal, was added to the reaction mixture, and the mixture was stirred at room temperature for 4.5 hours. Ice pieces were added thereto on the ice bath to decompose the excess reducing agent, and the solvent was distilled off under reduced pressure. The residue thereby obtained was extracted with chloroform. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried

over sodium sulfate, and then the solvent was distilled off to obtain 11.95 g of the above identified compound as a pale yellow semi-solid substance.

NMR($CDCl_3$) δ: 5.72 (1H, s), 4.00 (4H, s), 2.30 (2H, broad s, disappeared upon the addition of D_2O)

REFERENCE EXAMPLE 4A

<u>4-Methyl-5-chloro-3(2H)pyridazinone</u>



Into a 500 ml flask, 189 g of methylmagnesium bromide (1 mol/liter of an ether solution) was charged, and 10.0 g of 4,5-dichloro-3(2H)pyridazinone was gradually added thereto at a temperature of about 15°C. The mixture was stirred at a temperature of from 40 to 50°C for about 3 hours. The disappearance of the starting dichloropyridazinone was confirmed by thin layer chromatography (developer; ethyl acetate:acetone = 2:1, v/v), whereupon the reaction was terminated. The reaction solution was transferred to a separating funnel, and about 300 ml of a saturated sodium chloride aqueous solution was added thereto, and then the mixture was vigorously shaken. The aqueous layer was removed. The organic layer was washed with about 200 ml of water, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The brown crystals thereby obtained

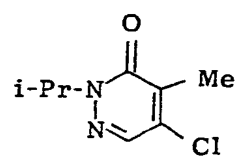
were recrystallized from ethyl acetate to obtain 4.54 g of the above identified compound having a melting point of from 132 to 134°C as colorless crystals.

NMR($CDCl_3$) δ: 2.27 (3H, s), 7.72 (1H, s), 12.52 (1H, broad s)

MS (m/e): 143(M^+)

REFERENCE EXAMPLE 5A

4-Methyl-5-chloro-2-i-propyl-3(2H)pyridazinone



Into a 200 ml four-necked flask, 4.54 g (0.032 mol) of 4-methyl-5-chloro-3(2H)pyridazinone prepared in Reference Example 4A, 6.34 g (0.038 mol) of isopropyl iodide and 60 ml of dimethylformamide were charged, and 1.66 g of sodium hydride (50% mineral oil suspension) was gradually added thereto at a temperature of about 5°C. The mixture was stirred at 30°C for about 3 hours.

The disappearance of the starting material was confirmed by thin layer chromatography (developer; chloroform), whereupon the reaction was terminated. 60 ml of benzene and 100 ml of a 10% hydrochloric acid aqueous solution were added thereto, and the mixture was vigorously shaken. The aqueous layer was removed. The organic layer was washed once with 50 ml of a saturated sodium chloride aqueous solution, and dried over anhydrous sodium salfate, and then the solvent was

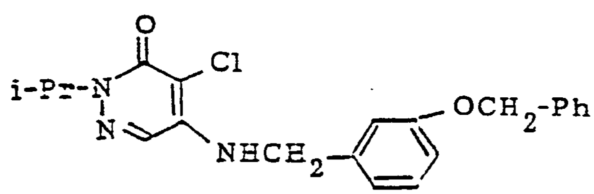
distilled off. The oily substance thereby obtained was separated and purified by silica gel column chromatography (developer; benzene:chloroform = 1:1 v/v) to obtain 2.85 g of the above identified compound.

Melting point: 40°C

NMR($CDCl_3$)δ: 7.76 (1H, s), 5.26 (1H, m), 2.27 (3H, s)
1.40 (3H, s), 1.29 (3H, s)

EXAMPLE 1A

4-Chloro-5-(3-benzyloxybenzylamino)-2-i-propyl-3-(2H)pyridazinone (Compound No. 95)



A mixture comprising 8.24 g of 3-benzyloxybenzylamine hydrochloride prepared in Reference Example 2A, 3.11 g of 2-i-propyl-4,5-dichloro-3(2H)pyridazinone, 7.26 g of potassium carbonate, 30 ml of 1,4-dioxane and 90 ml of water was refluxed under stirring for 4.5 hours. The majority of 1,4-dioxane was distilled off under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with diluted hydrochloric acid, and then treated with cerite to remove the precipitate. The organic layer was separated, and washed with water and a saturated sodium chloride aqueous solution, and then dried over sodium sulfate. Then, the solvent was distilled off. The pale yellow oily

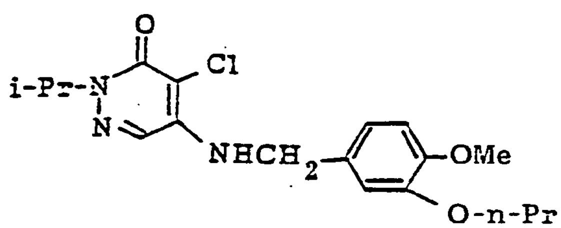
substanace thereby obtained was crystallized from ether-n-hexane to obtain 2.51 g of the above identified compound having a melting point of from 106 to 108°C as colorless crystals.

NMR($CDCl_3$)δ: 7.48 (1H, s), 7.30 (5H, s), 7.3-6.7 (4H, m), 5.02 (2H, s), 4.49, 4.40 (total 2H, each s), 5.2-4.8 (1H, broad s), 1.30 (6H, d)

MS (m/e): 383(M^+), 348, 91 (100%)

EXAMPLE 2A

<u>4-Chloro-5-(3-n-propoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone (Compound No. 106)</u>



A mixture comprising 1.34 g of 3-n-propoxy-4-methoxybenzylamine hydrochloride, 0.4 g of 4,5-dichloro-2-i-propyl-3(2H)pyridazinone, 1.08 g of potassium carbonate, 6 ml of 1,4-dioxane and 18 ml of water was refluxed under stirring for 8 hours. The solvent was distilled off under reduced pressure, and water was added to the the residue thereby obtained, and then the mixture was extracted with ethyl acetate. The extract was washed successively with diluted hydrochloric acid, water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off. The product was crystallized

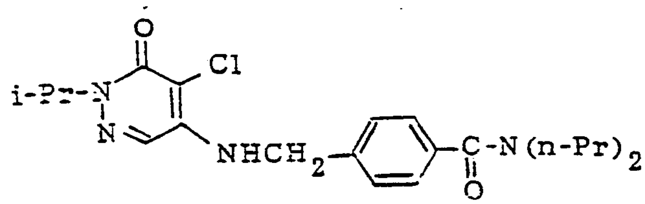
from ethyl acetate-diethyl ether-n-hexane to obtain 230 mg of the above identified compound having a melting point of from 120 to 122°C as colorless crystals.

NMR($CDCl_3$)δ: 7.58 (1H, s), 6.81 (3H, s), 5.38-4.93 (2H, m), 4.47, 4.37 (total 2H, each s), 3.94 (2H, t), 3.83 (3H, s), 2.05-1.65 (2H, m) 1.28 (6H, d), 1.02 (3H, t)

MS (m/e): 365(M^+), 330, 179 (100%), 137

EXAMPLE 3A

4-Chloro-5-(4-di-n-propylaminocarbonylbenzylamino)-2-i-propyl-3(2H)pyridazinone (Compound No. 125)



A mixture of 322 mg of 4-chloro-5-(4-carboxybenzylamino)-2-i-propyl-3(2H)pyridazinone obtained from 2-i-propyl-4,5-dichloro-3(2H)pyrisazinone and 4-carbonxybenzylamine, 194 mg of N,N'-carbonyldiimidazole and 5 ml of dimethylformamide, was stirred at room temperature for one hour. A solution obtained by dissolving 100 mg of di-n-propylamine in 1 ml of dimethylformamide was added thereto, and the mixture was stirred at the same temperature overnight. The solvent was distilled off under reduced pressure, and the pale yellow oily substance thereby obtained was extracted with chloroform. The extract was washed successively with

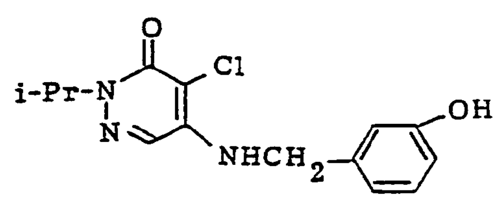
diluted hydrochloric acid, water, a 5% sodium hydroxide aqueous solution and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale yellow oily substance. This substance was subjected to silica gel column chromatography and eluted with benzene:ethyl acetate (2:5, v/v). The colorless viscous oily substance thereby obtained was crystallized from ether-n-hexane to obtain 108 mg of the above identified compound having a melting point of from 78 to 81°C as colorless crystals.

NMR($CDCl_3$)δ: 7.48 (1H, s), 7.28 (4H, s), 4.58, 4.48 (total 2H, each s), 3.7-2.9 (4H, m), 1.8-0.5 (10H, m), 1.29 (6H, d)

MS (m/e): 404(M^+), 304 (100%), 217, 100

EXAMPLE 4A

4-Chloro-5-(3-hydroxybenzylamino)-2-i-propyl-3-(2H)pyridazinone (Compound No. 137)



Into a mixture comprising 1.15 g of 4-chloro-5-(3-benzyloxybenzylamino)-2-i-propyl-3(2H)pyridazinone (Compound No. 95) prepared in Example 1A, 10 ml of dimethyl sulfide and 4 ml of dichloromethane, 3.41 g of boron trifluoride etherate was added under cooling with

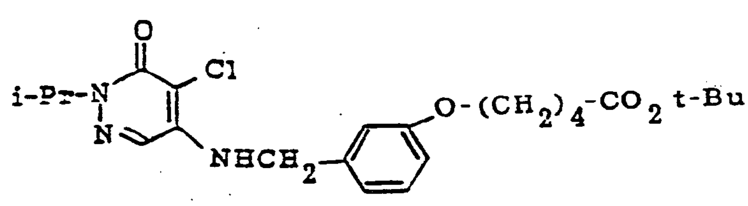
ice. The mixture was stirred at 0°C for 30 minutes and at room temperature for further 24 hours. The reaction solution was cooled with ice and 40 ml of n-hexane was added thereto, whereby a pale yellow solid substance was precipitated. The solid substance was collected by filtration, and washed with n-hexane, and then treated with ethyl acetate and water. The organic layer was separated, and washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale yellow solid substance. This substance was crystallized from ethyl acetate-ether to obtain 730 mg of the above identified compound having a melting point of from 194.5 to 196°C as colorless crystals.

NMR($CDCl_3$ + DMSO-d_6)δ: 7.51 (1H, s), 6.6-7.2 (4H, m), 6.3-5.8 (1H, broad s), 4.5, 4.4 (total 2H, each s), 1.26 (6H, d)

MS (m/e): 293(M^+), 258, 251, 216 (100%), 107

EXAMPLE 5A

4-Chloro-5-[3-(4-t-butoxycarbonyl)butoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 139)



A mixture comprising 2.056 g of 4-chloro-5-(3-hydroxybenzylamino)-2-i-propyl-3(2H)pyridazinone

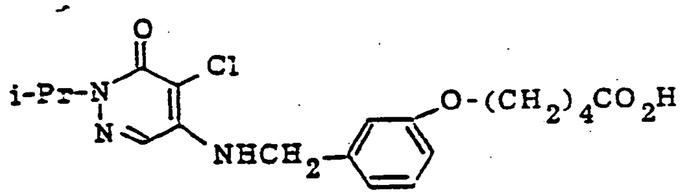
(Compound No. 137) prepared in Example 4A, 5.807 g of t-butyl 5-bromovalerate, 2.62 g of sodium iodide, 4.64 g of potassium carbonate and 50 ml of methyl ethyl ketone, was refluxed under stirring for 3 days. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain a pale violety red oily substance. This product was subjected to silica gel column chromatography, and the fraction eluted with benzene-ethyl acetate (3:1, v/v) was subjected to distillation to obtain 3.21 g of the above identified compound as a pale yellow viscous oily substance.

NMR($CDCl_3$) δ: 7.55 (1H, s), 7.4-6.7 (4H, m), 4.63, 4.52 (total 2H, each s), 1.43 (9H, s), 1.30 (6H, s)

MS (FD; m/e): 449(M^+)

EXAMPLE 6A

<u>4-Chloro-5-[3-(4-carboxy)butoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 142)</u>



In 30 ml of a 1,4-dioxane solution of 6N HCl, 3.00 g of 4-chloro-5-[3-(4-t-butoxycarbonyl)butoxybenzylamino]-

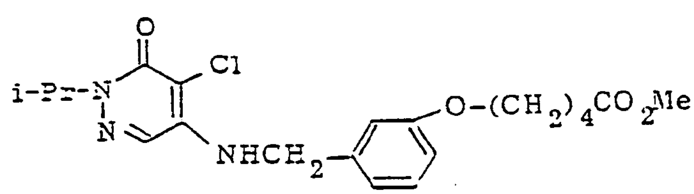
2-i-propyl-3(2H)pyridazinone (Compound No. 139) prepared in Example 5A was dissolved, and the mixture was stirred at room temperature for 50 minutes. The solvent was distilled off under reduced pressure. The dark yellowish orange oily substance thereby obtained was subjected to silica gel column chromatography, and eluted with chlroform-methanol (24:1, v/v) to obtain 1.75 g of the above identified compound as a colorless foamed substance.

NMR($CDCl_3$) δ: 7.51 (1H, s), 7.4-6.9 (1H, broad s, disappeared upon the addition of D_2O), 7.2-6.6 (4H, m), 4.50, 4.40 (total 2H, each s), 3.95 (2H, collapsed t), 2.42 (2H, collapsed t), 2.0-1.6 (4H, m), 1.30 (6H, d)

MS (FD; m/e): 394(M^++1)

EXAMPLE 7A

4-Chloro-5-[3-(4-methoxycarbonyl)butoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 144)



Into 30 ml of an ethyl acetate solution containing 1.30 g of 4-chloro-5-[3-(4-carboxy)butoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 142) prepared in Example 6A, diazomethane was bubbled until the solution was colored pale yellow, and the reaction solution was left to stand still overnight. The solvent

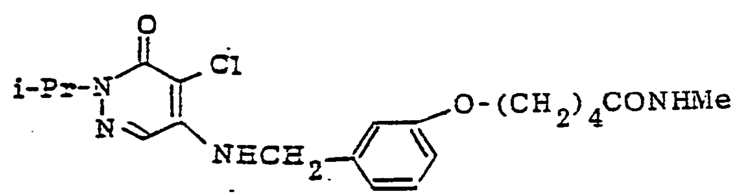
was distilled off to obtain 1.35 g of the above identified compound as a pale yellow oily substance.

NMR($CDCl_3$) δ: 7.51 (1H, s), 7.2-6.6 (4H, m), 4.51, 4.41 (total 2H, each s), 3.92 (2H, collapsed t), 3.62 (3H, s), 2.38 (2H, collapsed t), 2.0-1.5 (4H, m), 1.28 (6H, d)

MS (FD; m/e): 407(M^+)

EXAMPLE 8A

4-Chloro-5-[3-(4-N-methylaminocarbonyl)butoxy-benzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 146)



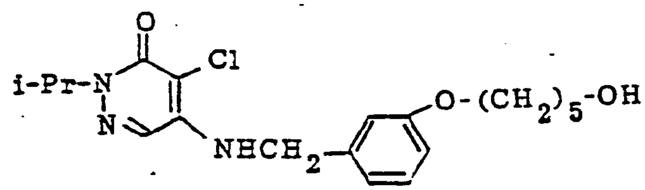
A mixture comprising 280 mg of 4-chloro-5-[3-(4-methoxycarbonyl)butoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone (Compound No. 144) prepared in Example 7A, 2.0 ml of methylamine (40% aqueous solution) and 2.0 ml of methanol, was stirred at room temperature for 2 days. The reaction solution was distilled off under reduced pressure, and the residue thereby obtained was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off to obtain 280 mg of the above identified compound as a pale yellow viscous oily substance.

NMR($CDCl_3$)δ: 7.51 (1H, s), 4.53, 4.43 (total 2H, each s), 3.91 (2H, collapsed t), 2.74 (3H, d), 2.5-1.6 (6H, m), 1.28 (6H, d)

MS (FD; m/e): 406(M^+)

EXAMPLE 9A

4-Chloro-5-[3-(5-hydroxy)pentoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 147)



Into 30 ml of a toluene solution containing 1.02 g of 4-chloro-5-[3-(4-methoxycarbonyl)butoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 144) prepared in Example 7A on the ice bath, 2.0 ml of a toluene solution containing 70% of sodium bis-methoxyethoxy-aluminum hydride was dropwise added, and the mixture was stirred for 1 hour. Diluted hydrochloric acid was gradually added to the reaction solution to decompose the excess reducing agent, and the mixture was extracted with chloroform. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium salfate, and then the solvent was distilled off to obtain a dark violety red oily substance. This substance was purified by silica gel column chromatography eluting with chloroform-methanol (25:1, v/v) to obtain 587 mg of the above identified compound as

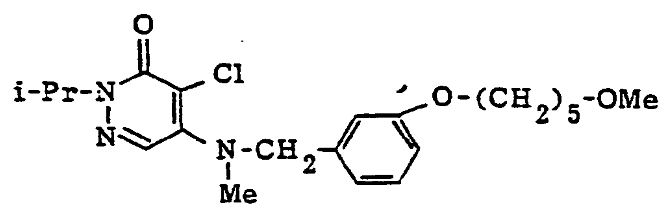
a pale yellow viscous oily substance.

NMR($CDCl_3$ + D_2O) δ: 7.50 (1H, s), 7.3-6.6 (4H, m), 4.51, 4.42 (total 2H, each s), 3.94 (2H, collapsed t), 3.64 (2H, collapsed t), 2.0-1.4 (6H, m), 1.29 (6H, d)

MS (FD; m/e): 379(M^+)

EXAMPLE 10A

<u>4-Chloro-5-[3-(5-methoxy)pentoxy-N-methylbenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 149)</u>



Into 10 ml of a tetrahydrofuran solution containing 420 mg of 4-chloro-5-[3-(5-hydroxy)pentoxybenzylamino]-2-i-propyl-3(2H)pyridazinone (Compound No. 147) prepared in Example 9A, 121 mg of sodium hydride (55% mineral oil -dispersed powder) was gradually added under cooling with ice, and the mixture was stirred for 10 minutes. 0.2 ml of methyl iodide was added thereto, and the mixture was stirred at the same temperature for 50 minutes. A 10% ammonium chloride aqueous solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and the solvent was distilled off to

obtain a pale yellow viscous oily substance. The substance was purified by silica gel column chromatography, whereby 40 mg of the above identified compound was obtained as a pale yellow viscous oily substance from the fraction initially eluted with benzene-ethyl acetate (1:1, v/v).

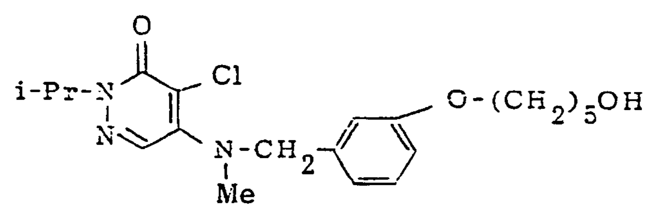
NMR($CDCl_3$)δ: 7.51 (1H, s), 7.3-6.6 (4H, m), 4.54 (2H, s), 3.92 (2H, collapsed t), 3.38 (2H, collapsed t), 3.29, 3.01 (each 3H, s), 2.0-1.4 (6H, m), 1.32 (6H, d)

MS (FD; m/e): 407(M^+)

EXAMPLE 11A

4-Chloro-5-[3-(5-hydroxy)pentoxy-N-methyl-benzyl-amino]-2-i-propyl-3(2H)pyridazinone

(Compound No. 150)



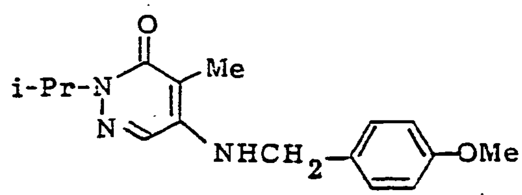
In the silica gel column chromatography operation in Example 10A, 403 mg of the above identified compound was obtained as a colorless viscous oily substance from the second fraction eluted with benzene-ethyl acetate (1:1, v/v).

NMR($CDCl_3$ + D_2O)δ: 7.59 (1H, s), 7.3-6.6 (4H, m), 4.52 (2H, s), 3.92 (2H, collapsed t), 3.62 (2H, collapsed t), 3.01 (3H, s), 2.0-1.4 (6H, m), 1.30 (6H, d)

MS (FD; m/e): 393(M^+)

EXAMPLE 12A

4-Methyl-5-(4-methoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone (Compound No. 151)



A mixture comprising 2.2 g of 4-methoxybenzylamine, 0.30 g of 4-methyl-5-chloro-2-i-propyl-3(2H)pyridazinone, 1.34 g of sodium hydrogencarbonate, 0.23 g of potassium carbonate and 5 ml of tri-n-propylamine, was heated at 150°C for 18 hours. The reaction mixture was acidified with a 10% hydrochloric acid aqueous solution, and extracted with 60 ml of benzene. The benzene layer was washed with water, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to obtain an oily substance. This substance was crystallized from 5 ml of ethyl ether to obtain 40 mg of the above identified compound.

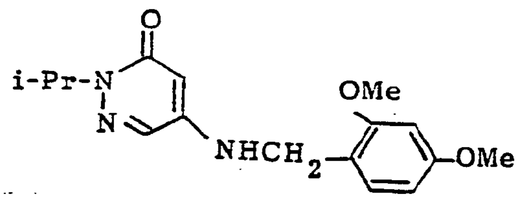
Melting point: 172 - 174°C

NMR($CDCl_3$)δ: 7.55 (1H, s), 4.41, 4.33 (total 2H, each s), 3.78 (3H, s), 1.98 (3H, s), 1.28 (6H, d)

MS (m/e): 287(M^+), 121 (100%)

EXAMPLE 13A

5-(2,4-dimethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone (Compound No. 100)



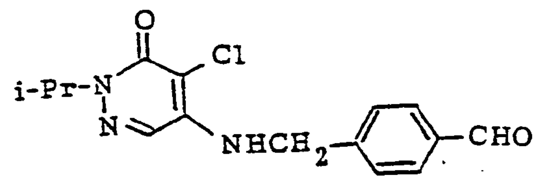
320 mg of 4-chloro-5-(2,4-dimethoxybenzylamino)-2-i-propyl-3(2H)pyridazinone (Compound No. 97), 50 ml of ethanol, 1 ml of triethylamine and 100 mg of palladium-carbon were stirred, and hydrogen was added to the mixture at a temperature of from 40 to 50°C for 3 hours. The reaction mixture was filtered, and the filtrate was evaporated. The crude crystals thereby obtained were recrystallized from ethyl ether to obtain 230 mg of the above identified compound having a melting point of from 167 to 168°C.

NMR($CDCl_3$) δ: 7.33 (1H, dd), 5.70 (1H, dd), 5.20 (1H, t), 4.80 (1H, broad), 4.20, 4.10 (total 2H, each s), 3.79 (3H, s), 3.75 (3H, s), 1.26 (6H, d)

MS (m/e): 305(M^+), 151 (100%)

EXAMPLE 14A

4-Chloro-5-(4-formylbenzylamino)-2-i-propyl-3(2H)-pyridazinone (Compound No. 140)



A mixture comprising 11.95 g of 4-(1,3-dioxoranyl)-benzylamine prepared in Reference Example 3A, 5.18 g of 2-i-propyl-4,5-dichloro-3(2H)pyridazinone, 4.15 g of potassium carbonate, 120 ml of water and 40 ml of 1,4-dioxane, was refluxed under stirring for 8 hours. The majority of 1,4-dioxane was distilled off under reduced pressure, and then the residue was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and the solvent was distilled off to obtain a pale yellow oily substance. This oily residue was dissoved in a mixed solution of 100 ml of tetrahydrofuran and 2 ml of water, and 4 ml of a dioxane solution of 6N HCl was added thereto. The mixture was stirred at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure, and diluted hydrochloric acid was poured into the residue, and then the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over sodium sulfate,

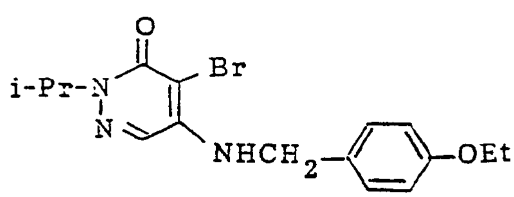
and then the solvent was distilled off to obtain a pale yellow oily substance. The substance was crystallized from ethyl acetate-ether-n-hexane to obtain 2.01 g of the above identified compound having a melting point of from 93.5 to 95°C as colorless crystals. The mother liquid for crystallization was concentrated, and subjected to silica gel column chromatography eluted with benzene-ethyl acetate (1:1, v/v) to further obtain 1.09 g (total yield: 3.10 g) of the above identified compound.

NMR($CDCl_3$) δ: 9.95 (1H, s), 7.85, 7.44 (4H, ABq) 7.45 (1H, s), 4.68, 4.58 (total 2H, each s) 1.28 (6H, d)

MS (m/e): 305(M^+), 263 (100%), 119

EXAMPLE 15A

<u>4-Bromo-5-(4-ethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone (Compound No. 164)</u>



A mixture of 0.38 g of 4-ethoxybenzylamine hydrochloride, 0.4 g of 4,5-dibromo-2-iso-propyl-3(2H)-pyridazinone, 0.34 g of potassium carbonate, 6 ml of 1,4-dioxane and 18 ml of water, was heated at 90°C under stirring for 10 hours. The sovent was distilled off under reduced pressure, and water was added to the residue thereby obtained, and the mixture was extracted

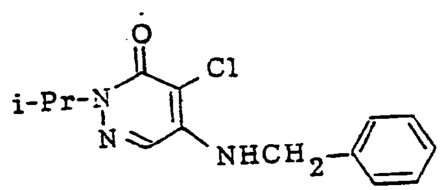
with ethyl acetate. The extract was washed with diluted hydrochloric acid and a saturated sodium chloride aqueous solution, and dried over sodium sulfate, and then the solvent was distilled off. The product was crystallized from ether to obtain 220 mg of the above identified compound having a melting point of from 151 to 152.5°C as pale yellow crystals.

NMR($CDCl_3$) δ: 7.68 (1H, s), 7.30, 6.96 (4H, ABq) 4.95-5.60 (2H, m), 4.58, 4.48 (total 2H, each s), 4.10 (2H, q), 1.50 (3H, t), 1.40 (6H, d)

MS (m/e): 365(M^+), 286, 244, 135 (100%)

EXAMPLE 16A

4-Chloro-5-(benzylamino)-2-i-propyl-3(2H)pyridazinone (Compound No. 74)



In 6 ml of dry dimethylformamide, 1.875 g of 4-chloro-5-amino-2-i-propyl-3(2H)pyridazinone was dissolved. 0.48 g of sodium hydride (50% mineral oil suspension) was added thereto at a temperature of from 5 to 10°C, and the mixture was stirred for about 30 minutes. Then, 1.4 g of benzyl chloride was dropwise added thereto at the same temperature. After the dropwise addition, the mixture was stirred at room temperature for 2 hours. To the reaction solution, 50 ml

of benzene and 30 ml of a 10% hydrochloric acid aqueous solution were added, and the mixture was vigorously shaken. The organic layer was washed with water, and dried, and then the solvent was distilled off. The crude crystals thereby obtained were recrystallized from ethyl ether to obtain 2.3 g of the above identified compound having a melting point of from 131 to 132°C.

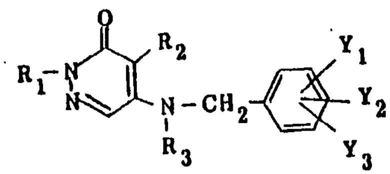
NMR($CDCl_3$) δ: 7.45 (1H, s), 5.08 (1H, broad s), 4.55, 4.46 (total 2H, each s), 1.26 (6H, d),

MS (m/e): 277(M^+), 235 (100%)

The compounds prepared in accordance with the above Examples are shown in Table 1A. In the right hand end column in the Table, the numbers of the Examples in accordance with which the respective compouds were prepared, are indicated.

Table 1A

Synthesis of



Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(°C)	MS (m/e)	Example No.
74	i-Pr	Cl	H	H	H	H	131 - 132	see Example 16A	16A
75	Et	Cl	H	3-Me	H	H	131 - 132	277 (M^+), 105 (100%)	2A
76	i-Pr	Cl	H	3-Me	H	H	149 - 149.5	291 (M^+), 105 (100%)	2A
77	i-Pr	Cl	H	4-Me	H	H	176	291 (M^+), 105 (100%)	2A
78	i-Pr	Cl	H	2-Me	H	H	146	291 (M^+), 105 (100%)	2A
79	Et	Cl	H	2-Me	4-Me	H	135 - 137	291 (M^+), 119 (100%)	2A
80	i-Pr	Cl	H	2-Me	4-Me	H	176 - 177	305 (M^+), 119 (100%)	2A
81	Et	Cl	H	4-Et	H	H	127	291 (M^+), 119 (100%)	2A
82	i-Pr	Cl	H	3-Et	4-OCH_2Ph	H	120 - 121	411 (M^+), 91 (100%)	1A
83	Et	Cl	H	3-Et	4-OCH_2Ph	H	144 - 145	397 (M^+), 91 (100%)	1A
84	i-Pr	Cl	H	3-Et	4-OMe	H	152 - 153	335 (M^+), 149 (100%)	2A
85	Et	Cl	H	3-Et	4-OMe	H	141 - 142	321 (M^+), 149 (100%)	2A

Table 1A(cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^{o}C)	MS (m/e)	Example No.
86	i-Pr	Cl	H	2-OMe	H	H	148 - 149.5	307 (M^+), 265 (100%)	2A
87	i-Pr	Cl	H	4-OMe	H	H	142	307 (M^+), 121 (100%)	2A
88	Et	Cl	H	3-OEt	H	H	131	307 (M^+), 272 (100%)	2A
89	i-Pr	Cl	H	3-OEt	H	H	136.5	321 (M^+), 135 (100%)	2A
90	Et	Cl	H	2-OEt	H	H	120 - 122	307 (M^+), 135 (100%)	2A
91	i-Pr	Cl	H	4-OEt	H	H	128 - 129	321 (M^+), 135 (100%)	2A
92	i-Pr	Cl	H	2-OEt	H	H	99	321 (M^+), 135 (100%)	2A
93	Et	Cl	H	3-O-n-Pr	H	H	96	321 (M^+), 286 (100%)	2A
94	i-Pr	Cl	H	3-O-n-Pr	H	H	119	335 (M^+), 300 (100%)	2A
95	i-Pr	Cl	H	3-OCH_2Ph	H	H	106 - 108	see Example 1A	1A
96	i-Pr	Cl	H	4-OCH_2Ph	H	H	140.5-141.5	383 (M^+), 91 (100%)	1A
97	i-Pr	Cl	H	2-OMe	4-OMe	H	125 - 126	337 (M^+), 151 (100%)	2A
98	i-Pr	Cl	H	3-OMe	5-OMe	H	139	337 (M^+), 302 (100%)	2A
99	Et	Cl	H	2-OMe	4-OMe	H	110 -111.5	323 (M^+), 151 (100%)	2A

Table 1A(cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	MS (m/e)	Example No.
100	i-Pr	H	H	2-OMe	4-OMe	H	167 - 168	see Example 13A	13A
101	i-Pr	Cl	H	2-OMe	3-OMe	H	121 -123	303 (M^+), 151 (100%)	2A
102	Et	Cl	H	3-OEt	4-OMe	H	134	337 (M^+), 165 (100%)	2A
103	i-Pr	Cl	H	3-OEt	4-OMe	H	112 - 113	351 (M^+), 165 (100%)	2A
104	i-Pr	Cl	H	2-OMe	5-OMe	H	123 - 124	337 (M^+), 151 (100%)	2A
105	Et	Cl	H	3-O-n-Pr	4-OMe	H	106.5-107.5	351 (M^+), 179 (100%)	2A
106	i-Pr	Cl	H	3-O-n-Pr	4-OMe	H	120 - 122	see Example 2A	2A
107	i-Pr	Cl	H	3-OMe	4-OEt	H	125	351 (M^+), 165 (100%)	2A
108	Et	Cl	H	3-OMe	4-O-n-Pr	H	112 - 113	351 (M^+), 137 (100%)	2A
109	i-Pr	Cl	H	2-OEt	4-OMe	H	113	351 (M^+), 165 (100%)	2A
110	Et	Cl	H	2-OMe	3-OEt	H	100 - 101.5	337 (M^+), 165 (100%)	2A
111	i-Pr	Cl	H	2-OMe	3-OEt	H	136 - 137	351 (M^+), 165 (100%)	2A
112	Et	Cl	H	2-O-n-Pr	4-OMe	H	oil	351 (M^+), 179 (100%)	2A
113	i-Pr	Cl	H	3-OEt	$4-OCH_2Ph$	H	112 - 113.5	427 (M^+), 91 (100%)	1A

Table 1A(cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	MS (m/e)	Example No.
114	i-Pr	Cl	H	2-OCH_2Ph	3-OEt	H	143 - 144	427 (M^+), 91 (100%)	1A
115	Et	Cl	H	3-OEt	4-OCH_2Ph	H	127 - 128	413 (M^+), 91 (100%)	1A
116	Et	Cl	H	2-OCH_2Ph	3-OEt	H	90	413 (M^+), 91 (100%)	1A
117	i-Pr	Cl	H	3-O-n-Pr	4-OCH_2Ph	H	104 - 104.5	441 (M^+), 91 (100%)	1A
118	Et	Cl	H	3-O-n-Pr	4-OCH_2Ph	H	145.5-146	427 (M^+), 91 (100%)	1A
119	i-Pr	Cl	H	3-O-, 4-O- CH_2		H	149.5-150.5	321 (M^+), 135 (100%)	2A
120	t-Bu	Cl	H	3-OMe	4-OMe	5-OMe	166	381 (M^+), 181 (100%)	2A
121	Et	Cl	H	3-OMe	4-OMe	5-OMe	170 - 172	353 (M^+), 181 (100%)	2A
122	i-Pr	Cl	H	3-OMe	4-OMe	5-OMe	177	367 (M^+), 181 (100%)	2A
123	i-Pr	Cl	H	4-Cl	H	H	152 - 152.5	311 (M^+), 125 (100%)	2A
124	Et	Cl	H	4-SMe	H	H	136 - 137	309 (M^+), 137 (100%)	2A
125	i-Pr	Cl	H	4-CON(n-Pr)(n-Pr)	H	H	78 - 81	see Example 3A	3A
126	n-Pr	Cl	H	4-N(Me)(Me)	H	H	127 - 128	320 (M^+), 134 (100%)	2A

Table 1A(cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^oC)	MS (m/e)	Example No.
127	i-Pr	Cl	H	2-OH	3-OEt	H	159 - 160	337 (M^+), 145 (100%)	4A
128	i-Pr	H	H	2-OH	3-OEt	H	214.5-215.5	303 (M^+), 111 (100%)	4A
129	Et	Cl	H	2-OH	3-OEt	H	179 - 180	323 (M^+), 145 (100%)	4A
130	i-Pr	Cl	H	4-OH	H	H	165 - 166	293 (M^+), 145 (100%)	4A
131	i-Pr	Cl	H	3-Et	4-OH	H	201 - 203	321 (M^+), 134 (100%)	4A
132	Et	Cl	H	3-Et	4-OH	H	171 - 172.5	307 (M^+), 134 (100%)	4A
133	i-Pr	Cl	H	3-O-n-Pr	4-OH	H	137 - 138	351 (M^+), 145 (100%)	4A
134	Et	Cl	H	3-O-n-Pr	4-OH	H	95 - 95.5	337 (M^+), 122 (100%)	4A
135	i-Pr	Cl	H	3-OEt	4-OH	H	183 - 184.5	337 (M^+), 145 (100%)	4A
136	Et	Cl	H	3-OEt	4-OH	H	153.5-154.5	323 (M^+), 145 (100%)	4A
137	i-Pr	Cl	H	3-OH	H	H	194.5-196	see Example 4A	4A
138	i-Pr	Cl	H	3-OH	4-OMe	H	175.5-176	323 (M^+), 137 (100%)	4A

Table 1A (cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^{o}C)	MS (m/e)	Example No.
139	i-Pr	Cl	H	3-O-$(CH_2)_4CO_2$ t-B_u	H	H	Viscous oily substance	see Example 5A	5A
140	i-Pr	Cl	H	4-CHO	H	H	93.5 - 95	see Example 14A	14A
141	i-Pr	Cl	H	3-O-$(CH_2)_4CO_2$ t-B_u	4-OMe	H	Viscous oily substance	479 (M^+), 237(100%)	5A
142	i-Pr	Cl	H	3-O-$(CH_2)_4CO_2H$	H	H	Viscous oily substance	see Example 6A	6A
143	i-Pr	Cl	H	3-O-$(CH_2)_4CO_2H$	4-OMe	H	Viscous oily substance	423 (M^+), 145 (100%)	6A
144	i-Pr	Cl	H	3-O-$(CH_2)_4CO_2Me$	H	H	Viscous oily substance	see Example 7A	7A
145	i-Pr	Cl	H	3-O-$(CH_2)_4CO_2Me$	4-OMe	H	94 -95	437 (M^+)	7A
146	i-Pr	Cl	H	3-O-$(CH_2)_4$CONHMe	H	H	Viscous oily substance	see Example 8A	8A
147	i-Pr	Cl	H	3-O-$(CH_2)_5OH$	H	H	Viscous oily substance	see Example 9A	9A
148	i-Pr	Cl	H	3-O-$(CH_2)_2$OMe	4-OMe	H	Simi-solid substance	381 (M^+), 195 (100%)	5A

Table 1A (cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(°C)	MS (m/e)	Example No.
149	i-Pr	Cl	Me	3-O-$(CH_2)_5$OMe	H	H	Viscous oily substance	see Example 10A	10A
150	i-Pr	Cl	Me	3-O-$(CH_2)_5$OH	H	H	Viscous oily substance	see Example 11A	11A
151	i-Pr	Me	H	4-OMe	H	H	172 - 174	see Example 12A	12A
152	i-Pr	Me	H	3-OEt	H	H	167 - 170	301 (M^+), 244 (100%)	12A
153	i-Pr	Me	H	3-O-n-Pr	4-OMe	H	127 - 128	345 (M^+), 179 (100%)	12A
154	Et	Br	H	4-OMe	H	H	96	337 (M^+), 121 (100%)	15A
155	Et	Br	H	4-OEt	H	H	87	351 (M^+), 135 (100%)	15A
156	Et	Br	H	3-OEt	H	H	108	351 (M^+), 272 (100%)	15A
157	Et	Br	H	3-O-n-Pr	H	H	88	365 (M^+), 286 (100%)	15A
158	Et	Br	H	2-Me	4-Me	H	131 -134	335 (M^+), 119 (100%)	15A
159	Et	Br	H	2-OMe	4-OMe	H	98	367 (M^+), 151 (100%)	15A
160	Et	Br	H	3-OEt	4-OMe	H	105	381 (M^+), 165 (100%)	15A

Table 1A (cont'd)

Compound No.	R_1	R_2	R_3	Y_1	Y_2	Y_3	mp(^{o}C)	MS (m/e)	Example No.
161	Et	Br	H	3-O-n-Pr	4-OMe	H	78	395 (M^+), 179 (100%)	15A
162	i-Pr	Br	H	4-OMe	H	H	131.5	351 (M^+), 121 (100%)	15A
163	i-Pr	Br	H	3-OMe	H	H	127.5	351 (M^+), 272 (100%)	15A
164	i-Pr	Br	H	4-OEt	H	H	151 - 152.5	see Example 15A	15A
165	i-Pr	Br	H	3-OEt	H	H	136 - 137.5	365 (M^+), 284 (100%)	15A
166	i-Pr	Br	H	3-OEt	4-OMe	H	115 - 117	395 (M^+), 165 (100%)	15A
167	i-Pr	Br	H	3-O-n-Pr	4-OMe	H	94 - 97	409 (M^+), 179 (100%)	15A
168	i-Pr	Br	H	2-Me	4-Me	H	171 - 173	349 (M^+), 119 (100%)	15A
169	i-Pr	Br	H	2-OMe	4-OMe	H	117	381 (M^+), 151 (100%)	15A

Now, Formulation Examples of the compounds of the formula I will be given.

FORMULATION EXAMPLE 1 (Tablets)

Compound No. 44	10 g
Lactose	20 g
Starch	4 g
Starch for paste	1 g
Magnesium stearate	100 mg
Carboxymethyl cellulose calcium	7 g
Total	42.1 g

The above components were mixed in a usual manner, and formulated into sugar-coated tablets each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 2 (Capsules)

Compound No. 15	10 g
Lactose	20 g
Crystal cellulose powder	10 g
Magnesium stearate	1 g
Total	41 g

The above components were mixed in a usual manner, and filled into a gelatin capsule to obtain capsules each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 3 (Soft capsules)

Compound No. 15	10 g
Corn oil	35 g
Total	45 g

The above components were mixed in a usual manner to obtain soft capsules.

FORMULATION EXAMPLE 4 (Ointment)

Compound No. 15	1.0 g
Olive oil	20 g
White vaseline	79 g
Total	100 g

The above components were mixed in a usual manner to obtain 1% ointment.

FORMULATION EXAMPLE 5 (Aerosol suspension)

(A)	
Compound No. 15	0.25 (%)
Isopropyl myristate	0.10
Ethanol	26.40
(B)	
A 60-40% mixture of 1,2-dichlorotetrafluoroethane and 1-chloropentafluoroethane	73.25

The above composition (A) was mixed. The solution mixture thereby obtained was charged in a container equipped with a valve, and the propellant (B) was injected from a valve nozzle to a gauge pressure of from about 2.46 to 2.81 kg/cm^2 to obtain an aerosol suspension.

FORMULATION EXAMPLE 6 (Tablets)

Compound No. 89	10 g
Lactose	20 g
Starch	4 g
Starch for paste	1 g
Magnesium stearate	100 mg
Carboxymethyl cellulose calcium	7 g
Total	42.1 g

The above components were mixed in a usual manner, and formulated into sugar-coated tablets each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 7 (Capsules)

Compound No. 87	10 g
Lactose	20 g
Crystal cellulose powder	10 g
Magnesium stearate	1 g
Total	41 g

The above components were mixed in a usual manner, and filled into a gelatin capsule to obtain capsules each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 8 (Soft capsules)

Compound No. 80	10 g
Corn oil	35 g
Total	45 g

The above components were mixed in a usual manner to obtain soft capsules.

FORMULATION EXAMPLE 9 (Ointment)

Compound No. 97	1.0 g
Olive oil	20 g
White vaseline	79 g
Total	100 g

The above components were mixed in a usual manner to obtain 1% ointment.

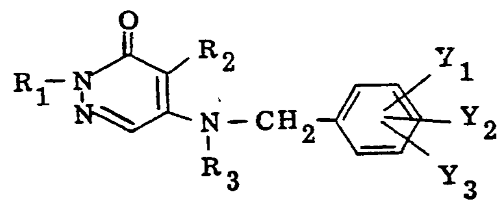
FORMULATION EXAMPLE 10 (Aerosol suspension)

(A)		
	Compound No. 105	0.25 (%)
	Isopropyl myristate	0.10
	Ethanol	26.40
(B)		
	A 60-40% mixture of 1,2-dichlorotetrafluoroethane and 1-chloropentafluoroethane	73.25

An aerosol suspension was prepared from the above composition (A) and the propellant (B) in accordance with Formulation Example 5.

CLAIMS:

1. A 3(2H)pyridazinone of the formula:



(I)

wherein R_1 is C_2-C_5 alkyl; R_2 is hydrogen, C_1-C_3 alkyl, chlorine or bromine; R_3 is hydrogen or C_1-C_4 alkyl; and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, halogen, $-(CH_2)_\ell A$ [wherein A is substituted amino of the formula $-N(R_4)(R_5)$ (wherein each of R_4 and R_5 which may be the same or different, is C_1-C_4 alkyl, or R_4 and R_5 together form C_4-C_6 alkylene), morpholino, 4-R_6-piperazin-1-yl (wherein R_6 is C_1-C_3 alkyl) or $-OR_7$ (wherein R_7 is hydrogen or C_1-C_3 alkyl), and ℓ is an integer of 0 to 3], $-OR_8$ [wherein R_8 is hydrogen, C_1-C_8 alkyl, C_3-C_5 alkenyl, benzyl or $-(CH_2)_q$-R_9 [wherein R_9 is CO_2R_3 (wherein R_3 is as defined above), $-CONHR_3$ (wherein R_3 is as defined above) or $-CH_2OR_7$ (wherein R_7 is as defined above), and q is an integer of 1 to 5]], $-CO_2R_3$ (wherein R_3 is as defined above), $-CON(R_{10})(R_{11})$ [wherein each of R_{10} and R_{11} which may be the same or different, is hydrogen, C_1-C_4 alkyl or C_3-C_5 alkenyl, or R_{10} and R_{11} together form C_4-C_6 alkylene, $-(CH_2)_2O(CH_2)_2-$ or

$-(CH_2)_2N(R_6)(CH_2)_2-$ (wherein R_6 is as defined above)], $-CONH(CH_2)_mA$ (wherein A is as defined above, and m is an integer of 2 to 4), $-CH{=}CHCOR_{12}$ (wherein R_{12} is hydroxy, C_1-C_4 alkoxy or $-N(R_{13})(CH_2)_nCO_2R_3$ (wherein R_{13} is hydrogen, C_1-C_6 alkyl or cycloalkyl, R_3 is as defined above, and n is an integer of 1 to 4)), $-SR_{14}$ (wherein R_{14} is C_1-C_4 alkyl), -CN or $-\underset{\underset{O}{\|}}{C}R_3$ (wherein R_3 is as defined above), or two of Y_1, Y_2 and Y_3 together form $\genfrac{}{}{0pt}{}{-O\diagdown}{\diagdown O\diagup}(CH_2)_p$ (wherein p is an interger of 1 or 2), and a pharmaceutically acceptable salt thereof.

2. The pyridazinone according to Claim 1, wherein R_2 is C_1-C_3 alkyl, chlorine or bromine, and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1-C_5 alkyl, halogen, $-CO_2R_3$ (wherein R_3 is as defined above), $-CON(R_{10})(R_{11})$ [wherein each of R_{10} and R_{11} which may be the same or different, is hydrogen, C_1-C_4 alkyl or C_3-C_5 alkenyl, or R_{10} and R_{11} together form $-(CH_2)_2O(CH_2)_2-$ or $-(CH_2)_2\underset{\underset{R_6}{|}}{N}(CH_2)_2-$ (wherein R_6 is as defined above)], $-OR_8$ [wherein R_8 is hydrogen, C_1-C_8 alkyl, $-(CH_2)_q-R_9$ (wherein R_9 is $-CO_2R_3$ (wherein R_3 is as defined above), $-CONHR_3$ (wherein R_3 is as defined above) or $-CH_2OR_7$ (wherein R_7 is as defined above) and q is as defined above], $-N(R_4)(R_5)$ (wherein R_4 and R_5 are as defined above), morpholino, 4-R_6-piperazin-1-yl (wherein R_6 is as defined above), $-SR_{14}$ (wherein R_{14} is as defined above), -CN or -CHO, or two of Y_1, Y_2 and Y_3 together form methylenedioxy.

3. The pyridazinone according to Claim 1, wherein R_1 is C_2-C_4 alkyl, R_2 is C_1-C_2 alkyl, chlorine or bromine, and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1-C_5 alkyl, halogen, $-CO_2R_3$ (wherein R_3 is as defined above), $-CON(R_{10})(R_{11})$ (wherein each of R_{10} and R_{11} which may be the same or different, is hydrogen or C_1-C_4 alkyl), $-OR_8$ (wherein R_8 is hydrogen or C_1-C_5 alkyl), dimethylamino, methylmercapto, -CN or -CHO, or two of Y_1, Y_2 and Y_3 together form methylenedioxy.

4. The pyridazinone according to Claim 1, wherein R_1 is C_2-C_4 alkyl, R_2 is methyl, chlorine or bromine, R_3 is hydrogen, and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1-C_3 alkyl, C_1-C_5 alkoxy or hydroxy, or two of Y_1, Y_2 and Y_3 together form methylenedioxy.

5. The pyridazinone according to Claim 1, wherein R_1 is ethyl or i-propyl, R_2 is methyl, chlorine or bromine, R_3 is hydrogen, Y_1 is hydrogen, and each of Y_2 and Y_3 which may be the same or different, is hydrogen, methyl, ethyl, methoxy, ethoxy, n-propoxy, or Y_2 and Y_3 together form methylenedioxy.

6. The pyridazinone according to Claim 1, which is
4-chloro-5-(2,4-dimethylbenzylamino)-2-ethyl-3(2H)-pyridazinone,
4-chloro-5-(3-ethyl-4-methoxybenzylamino)-2-ethyl-3(2H)-pyridazinone,
4-chloro-5-(3-ethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone,

4-chloro-5-(3-n-propoxybenzylamino)-2-ethyl-3(2H)-pyridazinone,

4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-2-ethyl-3(2H)pyridazinone,

4-chloro-5-(2,4-dimethylbenzylamino)-2-ethyl-3(2H)-pyridazinone,

4-chloro-5-(3-ethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-chloro-5-(4-ethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-chloro-5-(2,4-dimethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-chloro-5-(3,4-methylenedioxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-bromo-5-(4-methoxybenzylamino)-2-ethyl-3(2H)-pyridazinone,

4-bromo-5-(3-n-propoxy-4-methoxybenzylamino)-2-ethyl-3(2H)pyridazinone,

4-bromo-5-(2,4-dimethylbenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-chloro-5-(3,4-dimethoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-methyl-5-(4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-methyl-5-(3-ethoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-chloro-5-(3-ethyl-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-bromo-5-(3-n-propoxy-4-methoxybenzylamino)-2-i-propyl-3(2H)pyridazinone,

4-chloro-5-(4-methylbenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-chloro-5-(2,4-dimethoxybenzylamino)-2-ethyl-3(2H)-pyridazinone,

4-bromo-5-(2,4-dimethylbenzylamino)-2-ethyl-3(2H)-pyridazinone,

4-bromo-5-(2,4-dimethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-chloro-5-(3-hydroxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

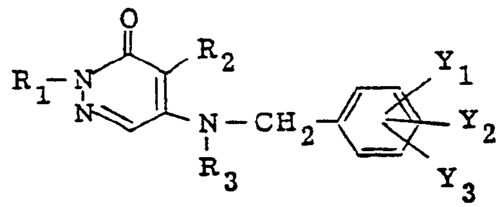
4-chloro-5-(2-ethoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-bromo-5-(4-methoxybenzylamino)-2-i-propyl-3(2H)-pyridazinone,

4-chloro-5-(3-methylbenzylamino)-2-ethyl-3(2H)-pyridazinone, or

4-chloro-5-(3-methylbenzylamino)-2-i-propyl-3(2H)-pyridazinone.

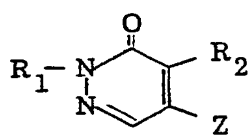
7. A process for producing a 3(2H)pyridazinone of the formula:



(I)

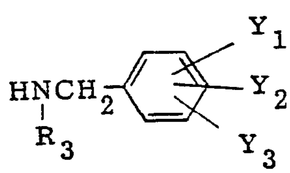
wherein R_1 is C_2-C_5 alkyl; R_2 is hydrogen, C_1-C_3 alkyl, chlorine or bromine; R_3 is hydrogen or C_1-C_4 alkyl; and each of Y_1, Y_2 and Y_3 which may be the same or different, is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, halogen, $-(CH_2)_{\ell}A$ [wherein A is substituted amino of the formula $-N(R_4)(R_5)$ (wherein each of R_4 and R_5 which may be the same or different, is C_1-C_4 alkyl, or R_4 and R_5 together form C_4-C_6 alkylene), morpholino, 4-R_6-piperazin-1-yl (wherein R_6 is C_1-C_3 alkyl) or $-OR_7$ (wherein R_7 is hydrogen or C_1-C_3 alkyl), and ℓ is an integer of 0 to 3], $-OR_8$ [wherein R_8 is hydrogen, C_1-C_8 alkyl, C_3-C_5 alkenyl, benzyl or $-(CH_2)_q$-R_9 [wherein R_9 is CO_2R_3 (wherein R_3 is as defined above), $-CONHR_3$ (wherein R_3 is as defined above) or $-CH_2OR_7$ (wherein R_7 is as defined above), and q is an integer of 1 to 5]], $-CO_2R_3$ (wherein R_3 is as defined above), $-CON(R_{10})(R_{11})$ [wherein each of R_{10} and R_{11} which may be the same or different, is hydrogen, C_1-C_4 alkyl or C_3-C_5 alkenyl, or R_{10} and R_{11} together form C_4-C_6 alkylene, $-(CH_2)_2O(CH_2)_2-$ or

$-(CH_2)_2N(R_6)(CH_2)_2-$ (wherein R_6 is as defined above)], $-CONH(CH_2)_mA$ (wherein A is as defined above, and m is an integer of 2 to 4), $-CH{=}CHCOR_{12}$ (wherein R_{12} is hydroxy, C_1-C_4 alkoxy or $-N(R_{13})(CH_2)_nCO_2R_3$ (wherein R_{13} is hydrogen, C_1-C_6 alkyl or cycloalkyl, R_3 is as defined above, and n is an integer of 1 to 4)), $-SR_{14}$ (wherein R_{14} is C_1-C_4 alkyl), -CN or $-\underset{\underset{O}{\|}}{C}R_3$ (wherein R_3 is as defined above), or two of Y_1, Y_2, and Y_3 together form $\genfrac{}{}{0pt}{}{-O}{-O}\!\!>(CH_2)_p$ (wherein p is an interger of 1 or 2), which comprises reacting a compound of the formula:



(II)

wherein R_1 and R_2 are as defined above and Z is chlorine or bromine, with a compound of the formula:



(III)

wherein R_3, Y_1, Y_2 and Y_3 are as defined above.

8. An anti-allergic agent comprising an effective amount of a 3(2H)pyridazinone of the formula I as defined in Claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. A method of reducing the incidence or severity of allergy induced in a subject by SRS-A, which comprises administering to said subject an amount effective to

reduce the incidence or severity of the allergy of a 3(2H)pyridazinone as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

0186817

EP 85115655.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	CHEMICAL ABSTRACTS, vol. 97, no. 7, August 16, 1982, Columbus, Ohio, USA MATSUO, TOSHIYASU; TSUKAMOTO, YOSHITSUGU; TAKAGI, TAKASHI; SATO, MAKOTO "Synthesis and biological activity of pyridazinooxazines" page 646, column 1, abstract-no. 55 755h & Chem. Pharm. Bull. 1982, 30(3), 832-42 --	1,8	C 07 D 237/22 A 61 K 31/50
X	CHEMICAL ABSTRACTS, vol. 89, no. 3, July 17, 1978, Columbus, Ohio, USA MATSUO, TOSHIYASU; TAKAGI, TAKASHI; TSUKAMOTO, YOSHITSUGU "Pyridazinone derivatives" page 656, column 1, abstract-no. 24 341a & Japan. Kokai 78 12,880 --	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 237/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-8

Claims searched incompletely: -

Claims not searched: 9

Reason for the limitation of the search:

Article 52(4) EPC, method for treatment of the human or animal body by therapy

Place of search	Date of completion of the search	Examiner
VIENNA	14-03-1986	HAMMER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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Application number

EP 85115655.4

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 78, no. 11, March 19, 1973, Columbus, Ohio, USA KARKLINA, A.; GUDRINIECE, E. "Reactions of 1-phenyl-4-nitro-5-chloro-6-pyridazone" page 466, column 1, abstract-no. 72 037a & Latv. PSR Zinat. Akad. Vestis, Kim. Ser. 1972 (6), 718-21 --	1	
A	US - A - 4 360 672 (PARG) * Formual I * ----	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)